Oxford Medicine





Drugs in Anaesthesia and Intensive Care (4 ed.)

Susan Smith, Edward Scarth, and Martin Sasada

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Preface to the fourth edition

The aims of this book remain true to those of the first edition. It continues in its original structured format; the major changes being the removal of agents no longer in use, the addition of new pharmacological drugs, and the introduction of summary chapters for drug families. We hope that this new edition will remain popular with critical care professionals, operating department personnel, paramedics, and anaesthetists of all grades in addition to providing sound examination preparation. Any comments will be gratefully received via e-mail (susan.smith@glos.nhs.uk and edscarth@doctors.org.uk).

S.P.S

E.J.S.

Cheltenham, May 2010









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Preface to the first edition

The aim of this book is twofold: firstly to summarize concisely the main pharmacodynamic and pharmacokinetic properties of the drugs with which the practising anaesthetist might be expected to be familiar. Secondly, it seeks to introduce the candidate for the FRCAnaes (and in particular, for the second part of this examination) to an ordered scheme for the presentation of information, which we have found to be of value in both the written and oral sections of the examinations. Examiners are more likely to turn a blind eye to minor errors or omissions of knowledge if they are in the context of a clear and well-ordered presentation. A further advantage of this scheme of presentation is that it allows rapid access to specific information. It is our hope that this compendium will prove to be a useful rapid source of reference for clinical anaesthetists in their day-to-day endeavours, both in the theatre and intensive care unit.

This book is intended to complement, rather than to replace, the standard texts on pharmacology for anaesthetists, since it includes no discussion of the principles of pharmacology, an understanding of which is essential for the clinical use of drugs. We feel that these aspects are very satisfactorily covered elsewhere.

Although our research has been as comprehensive as possible, there will obviously remain some information that will have eluded us, or perhaps remains to be discovered. Many practitioners will disagree with our choice of 172 drugs. Any comments or suggestions will be most gratefully and humbly received in order that further editions of this book may hopefully prove to be more useful.

Finally, we should like to thank the members of the Oxford Regional Drug Information Unit, the many drug company information departments, and all our colleagues for their help and support in this venture. In particular, we should like to thank Professor Roy Spector and Drs John Sear and Tim Peto for their invaluable advice on the manuscript.

M.P.S

S.P.S.

Oxford, 1990



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How to use this book

The layout of this book requires some explanation in order for the reader to gain the maximum benefit. The 172 drugs we have included are arranged in alphabetical order to obviate both reference to an index and artificial categorization of some drugs. Each drug is presented in an identical format and confined to one, two or three pages under the following headings:

Uses The main clinical uses are listed.

Chemical A brief chemical classification is given.

Presentation The formulations of the commercially available preparations are described.

Main action The fundamental pharmacological properties are briefly indicated.

Mode of action The mode of action at a cellular or molecular level (where known) is described.

Routes of administration/doses The manufacturer's recommended dose ranges are listed in this section; alternative clinical uses are also mentioned.

Effects The pharmacodynamic properties are systematically reviewed. Where a drug has no specific or known action on a particular physiological system, the relevant section has been omitted.

The systems described are:

CVS Cardiovascular system.

RS Respiratory system.

CNS Central nervous system.

AS Alimentary system.

GS Genitourinary system.

Metabolic/other Metabolic, endocrine, and miscellaneous.

Toxicity/side effects The major side effects are listed, with particular reference to the practice of anaesthesia and intensive care.

Kinetics The available pharmacokinetic data are provided. Quantitative data are not available for all drugs, particularly the long established ones. Where information on the absorption, distribution, metabolism,

or excretion is unavailable for a particular drug, the relevant section has been omitted.

Absorption Details of the absorption and bioavailability are given.

Distribution This section provides information on the volume of distribution and degree of protein binding of the drug, together with, where appropriate, details of central nervous penetration, transplacental passage, etc.

Metabolism The site and route of metabolic transformation and nature and activity of metabolites are described.

Excretion The excretory pathways, clearance, and elimination half-life are listed. Although clearances are usually expressed in ml/min/kg, this has not always been possible due to inadequacies in the original source material.

Special points This section describes points of relevance to the practice of anaesthesia and intensive care; in particular, significant drug interactions are reviewed.

This standard format offers great advantages; it enables specific questions to be answered very rapidly. For example, the question 'How is fentanyl metabolized?' may be answered simply by locating the drug alphabetically and then consulting the Metabolism section of the text. This principle holds true for all possible permutations of queries.




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Glossary of terms used in this book

%
percent
<
less than
>
greater than
°C
degree Celsius
®
registered
ACEI
angiotensin-converting enzyme inhibitor
ACT
activated coagulation time
ADH
antidiuretic hormone
ADHD
attention deficit hyperactivity disorder
ADP
adenosine diphosphate
ALT
alanine transaminase
AMP
adenosine monophosphate
APC
activated protein C
APTT
activated partial thromboplastin time
ARDS
acute respiratory distress syndrome
AS
abdominal system
ATP
adenosine triphosphate
AV
atrio-ventricular
Ca^{2+}
calcium ion
cAMP
cyclic adenosine monophosphate
cf.
confer (compare with)
cGMP
cyclic guanosine monophosphate
CNS
central nervous system
CO_2
carbon dioxide
COX

cyclo-oxygenase
CRP
C-reactive protein
CSF
cerebrospinal fluid
CVS
cardiovascular system
DIC
disseminated intravascular coagulation
DNA
deoxyribonucleic acid
DVT
deep vein thrombosis
ECG
electrocardiogram
EEG
electroencephalogram
e.g.
exempli gratia (for example)
EMLA
Eutectic Mixture of Local Anaesthetics
ESBL
extended spectrum beta-lactamase
ESR
erythrocyte sedimentation rate
FEV1
forced expiratory volume in first second
FiO2
partial pressure of oxygen in inspired air
FVC
forced vital capacity
g
gram
GABA
gamma-amino-butyric acid
GU
genitourinary
HAFOE
high air flow oxygen enrichment
HAS
human albumin solution
HDL
high-density lipoprotein
HepBsAg
hepatitis B surface antigen
HES
hydroxyethyl starches
HFIP
hexafluoroisopropanol
HIV
human immunodeficiency virus
HMGCoA
3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
5HT
5-hydroxytryptamine
Hz
Hertz
i.e.
id est (that is)
IgG
immunoglobulin G
IL-6
interleukin-6
INR
international normalized ratio
ITU
intensive treatment unit
IU
international unit
K+
potassium ion
kCal
kilocalorie
kg
kilogram
KIU
kallikrein inhibitory unit

KOH
potassium hydroxide
kPa
kilopascal
l
litre
LMA
laryngeal mask airway
LMWH
low molecular weight heparin
MAC
minimal alveolar concentration
MAOI
monoamine oxidase inhibitor
mb
millibar
MDMA
3,4-methylenedioxymethamphetamine
mEq
milliequivalent
µg
microgram
mg
milligram
min
minute
mL
millilitre
mmol
millimole
MOP
mu-opioid
mOsm
milliosmole
MRI
magnetic resonance imaging
mRNA
messenger ribonucleic acid
MRSA
meticillin-resistant *Staphylococcus aureus*
mUnit
milliunit
Na^+
sodium ion
NAC
N-acetylcysteine
NaOH
sodium hydroxide
NAPQI
N-acetyl-p-benzo-quinoneimine
ng
nanogram
nm
nanometre
NMB
neuromuscular blocking
NMDA
N-methyl-D-aspartate
NO
nitric oxide
N_2O
nitrous oxide
NSAID
non-steroidal anti-inflammatory drug
$PaCO_2$
partial pressure of carbon dioxide in arterial blood
PaO_2
partial pressure of oxygen in arterial blood
PBP
penicillin-binding protein
PEFR
peak expiratory flow rate
PIFE
pentafluoroisopropenyl fluoromethyl ether
PMFE
pentafluoromethoxy isopropyl fluoromethyl ether
PONV

post-operative nausea and vomiting
ppm
part per million
PVR
pulmonary vascular resistance
q.v.
quod vide (which see)
REM
rapid eye movement
RNA
ribonucleic acid
RS
respiratory system
rtPA
recombinant tissue plasminogen activator
SA
sinoatrial
spp
species
SSRI
specific serotonic re-uptake inhibitor
STP
standard temperature and pressure
TPN
total parenteral nutrition
tRNA
transfer ribonucleic acid
UK
United Kingdom
USA
United States of America
V_D
volume of distribution
VD_{SS}
volume of distribution at steady state
VIE
vacuum-insulated evaporator
VMA
vanillylmandelic acid
vpm
volume per million
VRE
vancomycin-resistant Enterococcus
vWF
von Willebrand factor
w/v
weight per volume
w/w
weight per weight





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A

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ACE Inhibitors

Uses

Angiotensin-converting enzyme inhibitors (ACEI) are used in the treatment of:

1. essential and renovascular hypertension
2. congestive cardiac failure
3. diabetic nephropathy.

Chemical

ACEI are derived from peptides originally isolated from the venom of the pit viper, *Bothrops jararaca*.

Presentation

ACEI are available in tablet or capsule form and a number of commercially available types are available, including captopril, enalapril, perindopril, lisinopril, and ramipril.

Main action

Antihypertensive.

Mode of action

ACEI inhibit angiotensin-converting enzyme (with an affinity many times greater than that of angiotensin I), so preventing the formation of angiotensin I from angiotensin II. Part of their action may also be exerted through the modulation of sympathetic tone or the kallikrein-kinin-prostaglandin system.

Route of administration/doses

ACEI are only currently available for oral administration. The specific dose and frequency of an agent administered is dependent on the clinical indication, age of the patient, and the particular agent being used.

Effects

CVS

The systemic vascular resistance decreases, leading to a decrease in the systolic and diastolic blood pressure; cardiac output may increase by up to 25%, especially in the presence of cardiac failure.

GU

ACEI cause an increase in renal blood flow although the glomerular filtration rate remains unchanged. A natriuresis may ensue, but there is little overall effect on plasma volume.

Toxicity/side effects

ACEI are generally well tolerated; hypotension, dizziness, fatigue, dry cough (due to an accumulation of bradykinin), gastrointestinal upsets, and rashes may occur. Renal function may deteriorate in patients with renovascular hypertension.

Kinetics

Data are incomplete.

Absorption

ACEI are reasonably well absorbed from the gastrointestinal tract. Bioavailability for individual drugs is as follows: captopril (75%), enalapril (40%), perindopril (75%), lisinopril (25%), ramipril (50–60%).

Distribution

The percentage of drug bound to plasma proteins is variable: captopril (30%), enalapril (50%), perindopril (76%), ramipril (73%).

Metabolism

Captopril undergoes metabolism to a disulphide dimer and cysteine disulphide. Enalapril and perindopril are pro-drugs that are metabolized to their respective active forms. ACEI undergo minimal metabolism in man.

Excretion

ACEI have markedly variable half-lives and clearance data. The half-life of captopril is 1.9 hours whereas that of lisinopril is 12 hours, enalapril 35 hours, perindopril 30–120 hours, and ramipril greater than 50 hours. Captopril has a low clearance compared to enalapril and perindopril which have plasma clearance values of approximately 300 ml/min.

Special points

The hypotensive effects of ACEI are additive with that of anaesthetic agents. However, they do not necessarily protect against the cardiovascular responses to laryngoscopy.

There is an increased risk of renal failure with the co-administration of ACEI and non-steroidal anti-inflammatory drugs (NSAIDs) in the presence of hypovolaemia.

Acetazolamide

Uses

Acetazolamide is used in the treatment of:

1. glaucoma
2. petit mal epilepsy
3. Meniere's disease
4. familial periodic paralysis and
5. the prophylaxis and treatment of altitude sickness.

Chemical

A sulphonamide.

Presentation

As 250 mg tablets of acetazolamide and in vials containing 500 mg of the sodium salt of acetazolamide for reconstitution with water prior to injection.

Main Action

Diuresis and a decrease in intraocular pressure.

Mode of Action

Acetazolamide is a reversible, non-competitive inhibitor of carbonic anhydrase situated within cell cytosol and on the brush border of the proximal convoluted tubule. This enzyme catalyses the conversion of bicarbonate and hydrogen ions into carbonic acid and then carbonic acid to carbon dioxide and water. Under normal circumstances, sodium ions are reabsorbed in exchange for hydrogen ions in the prox-imal and distal renal tubules; aceta-zolamide decreases the availability of hydrogen ions and therefore sodium and bicarbonate ions remain in the renal tubule, leading to a diuresis.

Route of Administration/Dose

The adult oral and intravenous dose is 250–1000 mg in divided doses.

Effects

RS

Acetazolamide produces a compensatory increase in ven-tilation in response to the metabolic acidosis and increased tissue carbon dioxide that the drug causes.

CNS

Acetazolamide has demonstrable anticonvulsant properties, pos-sibly related to an elevated carbon dioxide tension within the central nervous system. The drug decreases the pressure of both the cerebrospinal fluid and the intraocular compartment by de-creasing the rate of formation of cerebrospinal fluid and aqueous humour (by 50–60%).

AS

The drug inhibits gastric and pancreatic secretion.

GU

Acetazolamide produces a mild diuresis, with retention of sodium ions and a subsequent increase in plasma sodium ion concentra-tion. The drug also decreases renal excretion of uric acid.

Metabolic/Other

The excretion of an alkaline urine results in the development of a hyperchloraemic metabolic acidosis in response to the administration of acetazolamide. The drug also interferes with iodide uptake by the thyroid.

Toxicity/Side Effects

Occur rarely, and include gastro-intestinal and haemopoietic disturbances, rashes, renal stones and hypokalaemia.

Kinetics

Absorption

Acetazolamide is rapidly and well absorbed when administered orally; the bioavailability by this route is virtually 100%.

Distribution

The drug is 70–90% protein-bound in the plasma.

Metabolism

Acetazolamide is not metabolised in man.

Excretion

The drug is excreted unchanged in the urine; the clearance is 2.7 l/hour and the elimination-half-life is 1.7–5.8 hours.

Special Points

The use of acetazolamide is contraindicated in the presence of hepatic or renal failure, as the drug will worsen any metabolic acidosis and may also cause urolithiasis. Pretreatment with the drug will obtund the increase in intraocu-lar pressure produced by the administration of suxamethonium; however, the use of aceta-zolamide is of dubious value during eye surgery as it simultaneously increases intrachoroidal vascu-lar volume. Aceta-zolamide has been used effectively for the correction of metabolic alkalosis in the critically ill.

Acetazolamide is removed by haemodialysis.

Aciclovir

Uses

Aciclovir is used in the treatment of:

1. *Herpes simplex* infections of the skin and eye
2. *Herpes simplex* encephalitis
3. recurrent *Varicella zoster* virus infections and
4. for the prophylaxis of *Herpes simplex* infections in immunocompromised patients.

Chemical

An analogue of the nucleoside 2'-deoxyguanosine.

Presentation

As 200/400/800 mg tablets, a suspension containing 40 mg/ml, a white lyophilized powder in vials containing 250 mg of aciclovir sodium which is reconstituted prior to injection in water, and as a 3% ophthalmic ointment and 5% w/w cream for topical application.

Main action

Aciclovir is an antiviral agent, active against *Herpes simplex* (I and II) and *Varicella zoster* virus.

Mode of action

Aciclovir is activated within the viral cell via phosphorylation by a virus-coded thymidine kinase and thus has a low toxicity for normal cells. Aciclovir triphosphate inhibits viral DNA polymerase by becoming incorporated into the DNA primer template, effectively preventing further elongation of the viral DNA chain.

Route of administration/doses

The adult oral dose is 200–400 mg 2–5 times daily, initially for a period of 5 days. The corresponding intravenous dose is 5–10 mg/kg 8-hourly, infused over a period of 1 hour. A higher dose is used for zoster than for simplex infections. Topical application should be performed 5 times daily, again for an initial period of 5 days.

Effects

Metabolic/other

Increases in plasma levels of urea and creatinine may occur if the drug is administered intravenously too rapidly.

Toxicity/side effects

Aciclovir is generally well tolerated. Central nervous system disturbances (including tremors, confusion, and seizures) and gastrointestinal upset may occur. Precipitation of the drug in the renal tubules leading to renal impairment may occur if the drug is administered too rapidly or if an adequate state of hydration is not maintained. The drug is an irritant to veins and tissues.

Kinetics

Absorption

Oral absorption of the drug is erratic; the bioavailability by this route is 15–30%.

Distribution

The drug is 9–33% protein-bound in the plasma; the V_D is 0.32–1.48 l/kg.

Metabolism

The major metabolite is 9-carboxymethoxymethyl guanine which is inactive.

Excretion

The drug is excreted by active tubular secretion in the urine, 45–80% unchanged. The elimination half-life is 2–3 hours.

Special points

A reduced dose should be used in the presence of renal impairment; haemodialysis removes 60% of the drug.

Adenosine

Uses

Adenosine is used in the diagnosis and treatment of paroxysmal supraventricular tachycardia.

Chemical

A naturally occurring nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA.

Presentation

As a clear, colourless solution containing 3 mg/ml adenosine in saline.

Main action

Depression of sinoatrial and atrio-ventricular nodal activity and slowing of conduction. The drug also antagonizes cAMP-mediated catechol stimulation of ventricular muscle. Both actions result in negative chronotropic and inotropic effects.

Mode of action

Adenosine acts as a direct agonist at specific cell membrane receptors, classified into A1 and A2 subsets. A1 receptors are coupled to potassium channels by a guanine nucleotide-binding protein in supraventricular tissue.

Route of administration/doses

Adenosine is administered as a rapid intravenous bolus, followed by a saline flush. The initial adult dose is 3 mg, followed, if necessary, by a 6 mg and then a 12 mg bolus at 1–2 minute intervals until an effect is observed. The paediatric dose is 0.0375–0.25 mg/kg. The drug acts within 10 seconds and has duration of action of 10–20 seconds.

Effects

CVS

Depression of sinoatrial and atrio-ventricular nodal activity leads to the termination of paroxysmal supraventricular tachycardia. Atrial dysrhythmias are revealed by atrio-ventricular nodal block, leading to a transient slowing of ventricular response. Adenosine has no clinically important effects on blood pressure when administered as a bolus. A continuous high-dose infusion may result in a decrease in systemic vascular resistance and decreased blood pressure. When administered as an infusion, adenosine causes a dose-dependent reflex tachycardia and an increase in cardiac output. The drug also causes a dose-dependent increase in myocardial blood flow secondary to coronary vasodilation mediated via endothelial A2 receptors. Adenosine decreases PVR in patients with pulmonary hypertension.

RS

Bolus administration of adenosine leads to an increase in both the depth and rate of respiration, probably mediated by A2 receptor stimulation in the carotid body. Infusion of the drug results in a fall in PCO_2. Bronchospasm may occur.

CNS

Infusion of adenosine results in increased cerebral blood flow. Low-dose adenosine induces neuropathic pain, hyperalgesia, and ischaemic pain. Adenosine itself is a neurotransmitter.

GU

Hypotensive doses of adenosine stimulate A2 receptors, resulting in renal and hepatic arterial vasoconstriction, although low doses have no effect on the glomerular filtration rate or sodium excretion.

Metabolic/other

Adenosine inhibits lipolysis and stimulates glycolysis.

Toxicity/side effects

The most common side effects are transient facial flushing, dyspnoea, and chest discomfort. Bronchospasm has also been reported. The induced bradycardia predisposes to ventricular excitability and may result in ventricular fibrillation. Profound bradycardia requiring pacing may occur.

Kinetics

Absorption

Adenosine is inactive when administered orally.

Metabolism

Exogenous adenosine is absorbed from the plasma into red blood cells and vascular endothelium, where it is phosphorylated to AMP or deaminated to inosine and hypoxanthine. The plasma half-life is less than 10 seconds.

Special points

No dose adjustment is necessary in the presence of renal or hepatic impairment. Adenosine has been used to induce hypotension perioperatively.

Intraoperative use of adenosine decreases the MAC of isoflurane and decreases post-operative analgesic requirements.

Adrenaline

Uses

Adrenaline is used in the treatment of:

1. anaphylactic and anaphylactoid shock
2. asystole
3. low cardiac output states
4. glaucoma and
5. as a local vasoconstrictor and
6. is added to local anaesthetic solutions to prolong their duration of action.

Chemical

A catecholamine.

Presentation

As a clear, solution for injection containing 0.1/1 mg/ml of adrenaline hydrochloride, a 1% ophthalmic solution, and as an aerosol spray delivering 280 micrograms metered doses or adrenaline acid tartrate.

Main action

Sympathomimetic.

Mode of action

Adrenaline is a directly acting sympathomimetic amine that is an agonist of alpha- and beta-adrenoreceptors; it has approximately equal activity at both alpha- and beta-receptors.

Routes of administration/doses

The drug may be administered intravenously either as an intravenous bolus in doses of 0.1–1 mg for the treatment of asystole or as an infusion at the rate of 0.01–0.1 micrograms/kg/min, titrated according to response; low doses tend to produce predominantly beta-effects whilst higher doses tend to produce predominantly alpha-effects. The dose by the subcutaneous route is 0.1–0.5 mg. Adrenaline may be administered by inhalation; a maximum daily dose of 10–20 metered doses is recommended.

Effects

CVS

Adrenaline is both a positive inotrope and a positive chronotrope and therefore, causes an increase in cardiac output and myocardial oxygen consumption. The drug causes an increase in coronary blood flow. When administered as an intravenous bolus, adrenaline markedly increases peripheral vascular resistance, producing an increase in systolic blood pressure with a less marked increase in diastolic blood pressure. When administered as an intravenous infusion, the peripheral vascular resistance (a direct beta-2 effect) and diastolic blood pressure both tend to decrease. The heart rate initially increases and subsequently decreases due to a vagal reflex. The plasma volume decreases as a result of the loss of protein-free fluid into the extracellular fluid. Adrenaline increases platelet adhesiveness and blood coagulability (by increasing the activity of factor V).

RS

Adrenaline is a mild respiratory stimulant and causes an increase in both the tidal volume and respiratory rate. The drug is a potent bronchodilator, but tends to increase the viscosity of bronchial secretions.

CNS

Adrenaline only penetrates the central nervous system to a limited extent, but does have excitatory effects. The drug increases the cutaneous pain threshold and enhances neuromuscular transmission. Adrenaline has little overall effect on cerebral blood flow. It has weak mydriatic effects when applied topically to the eye.

AS

The drug decreases intestinal tone and secretions; the splanchnic blood flow is increased.

GU

Adrenaline decreases renal blood flow by up to 40% although the glomerular filtration rate remains little altered. The bladder tone is decreased and the sphincteric tone increased by the drug, which may lead to difficulty with micturition. Adrenaline inhibits the contractions of the pregnant uterus.

Metabolic/other

The drug has profound metabolic effects; it decreases insulin secretion whilst increasing both glucagon secretion and the rate of glycogenolysis, resulting in elevation of the blood sugar concentration. The plasma renin activity is increased by the drug (a beta-1 effect) and the plasma concentration of free fatty acids is increased by the activation of triglyceride lipase. The serum potassium concentration transiently rises (due to release from the liver) following the administration of adrenaline; a more prolonged decrease in potassium concentration follows. Adrenaline administration increases the basal metabolic rate by 20–30%; in combination with the cutaneous vasoconstriction that the drug produces, pyrexia may result.

Toxicity/side effects

Symptoms of central nervous system excitation, cerebral haemorrhage, tachycardia, dysrhythmias, and myocardial ischaemia may result from the use of adrenaline.

Kinetics

Data are incomplete.

Absorption

The drug is inactivated when administered orally. Absorption is slower after subcutaneous than intramuscular administration. The drug is well absorbed from the tracheal mucosa.

Metabolism

Exogenous adrenaline is predominantly first metabolized by catechol-O-methyl transferase predominantly in the liver to metadrenaline and normetadrenaline (uptake-2); some is metabolized by monoamine oxidase within adrenergic neurones (uptake-1). The final common products of adrenaline metabolism are 3-methoxy 4-hydroxyphenylethylene and 3-methoxy 4-hydroxymandelic acid (which are inactive).

Excretion

The inactive products appear predominantly in the urine.

Special points

The dose of adrenaline should be limited to 1 micrograms/kg/30 minutes in the presence of halothane and to 3 micrograms/kg/30 minutes in the presence of enflurane or isoflurane in an attempt to prevent the appearance of serious ventricular dysrhythmias. Infiltration of adrenaline-containing solutions should be avoided in regions of the body supplied by end arteries.

Alfentanil

Uses

Alfentanil is used:

1. to provide the analgesic component in general anaesthesia
2. sedation regimens for intensive care and
3. to obtund the cardiovascular responses to laryngoscopy.

Chemical

A synthetic phenylpiperidine derivative.

Presentation

As a clear, colourless solution for injection containing 0.5/5 mg/ml of alfentanil hydrochloride. The pKa of alfentanil is 6.5; alfentanil is 89% unionized at a pH of 7.4 and has a relatively low lipid solubility. Despite the low lipid solubility of the drug (octanol:water partition coefficient of 128.1), it has a faster onset of action compared to fentanyl which has much higher lipid solubility due to its low pKa and consequently large amount of unionized drug available to cross lipid membranes.

Main actions

Analgesia and respiratory depression.

Mode of action

Alfentanil is a highly selective mu-opioid (MOP) agonist; the MOP receptor appears to be specifically involved in the mediation of analgesia. Opioids appear to exert their effects by interacting with pre-synaptic Gi protein receptors, leading to a hyperpolarization of the cell membrane by increasing potassium conductance. Inhibition of adenylate cyclase, leading to a reduced production of cyclic adenosine monophosphate and closure of voltage-sensitive calcium channels also occurs. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routes of administration/doses

Alfentanil is administered intravenously in boluses of 5–50 micrograms/kg. The drug may be administered by intravenous infusion at a rate of 0.5–1 micrograms/kg/min. Alfentanil acts rapidly with the peak effect occurring within 90 seconds of intravenous administration and the duration of effect is 5–10 minutes. Administration of alfentanil

reduces the amount of hypnotic/volatile agents required to maintain anaesthesia.

Effects

CVS

The most significant cardiovascular effect that alfentanil demonstrates is bradycardia of vagal origin; cardiac output, mean arterial pressure, pulmonary and systemic vascular resistance, and pulmonary capillary wedge pressure are unaffected by the administration of the drug. Doses of 5 micrograms/kg increase left ventricular contractility and cardiac output in animal models. Alfentanil obtunds the cardiovascular responses to laryngoscopy and intubation.

RS

Alfentanil is a potent respiratory depressant, causing a decrease in both the respiratory rate and tidal volume; it also diminishes the ventilatory response to hypoxia and hypercarbia. The drug is a potent antitussive agent. Chest wall rigidity (the 'wooden chest' phenomenon) may occur after the administration of alfentanil—this may be an effect of the drug on mu (MOP) receptors located on GABA-ergic interneurons. Alfentanil causes minimal histamine release; bronchospasm is thus rarely produced by the drug.

CNS

Alfentanil is 10 to 20 times more potent an analgesic than morphine and has little hypnotic or sedative activity. Miosis is produced as a result of stimulation of the Edinger–Westphal nucleus. Alfentanil reduces intraocular pressure by approximately 45%. The drug causes an increase in the amplitude of the EEG and reduces its frequency.

AS

The drug decreases gastrointestinal motility and gastric acid secretion; it also doubles the common bile duct pressure by causing spasm of the sphincter of Oddi.

GU

Alfentanil increases the tone of the ureters, bladder detrusor muscle, and vesicular sphincter.

Metabolic/other

High doses of alfentanil will obtund the metabolic 'stress response' to surgery; the drug appears to be even more effective than fentanyl in this respect. Unlike morphine, alfentanil does not increase the activity of antidiuretic hormone.

Toxicity/side effects

Respiratory depression, bradycardia, nausea, vomiting, and dependence may also complicate the use of the drug.

Kinetics

Distribution

Alfentanil is 85–92% bound to plasma proteins, predominantly to alpha-1 acid glycoprotein; the V_D is 0.4–1 l/kg. Alfentanil crosses the placenta.

Metabolism

Alfentanil is predominantly metabolized in the liver by N-dealkylation to noralfentanil; the remainder of the drug is metabolized by a variety of pathways, including aromatic hydroxylation, demethylation, and amide hydrolysis followed by acetylation. The major phase II pathway is by conjugation to glucuronide. Cytochrome P450 3A3 and 3A4 play a predominant role in alfentanil metabolism and may be subject to competitive inhibition by the co-administration of midazolam, which may lead to a prolongation of alfentanil and midazolam drug effects. Metabolism of the drug may also be prolonged when other CYP3A4 inhibitors are used concomitantly.

Excretion

90% of an administered dose is excreted in the urine (<1% as unchanged drug). The clearance of alfentanil is 3.3–8.3 ml/kg/min and the elimination half-life range is 90–111 minutes. The relatively brief duration of action of a single dose of alfentanil in comparison to that of fentanyl is due to the smaller volume of distribution and shorter elimination half-life of the former.

Special points

Alfentanil decreases the apparent MAC of co- administered volatile agents. The concomitant use of erythromycin, cimetidine, fluconazole, ketoconazole, ritonavir, and diltiazem may significantly inhibit the clearance of alfentanil.

The half-life of the drug is prolonged in the elderly and debilitated patients and those with significant hepatic and renal impairment.

It is unknown whether alfentanil is removed by haemodialysis.

Allopurinol

Uses

Allopurinol is used:

1. in the prophylaxis of gout
2. to prevent renal stone formation in patients with xanthinuria and
3. in the prophylaxis of the tumour lysis syndrome.

Chemical

A hypoxanthine analogue.

Presentation

As 100/300 mg tablets of allopurinol.

Main action

Xanthine oxidase inhibitor and free-radical scavenger.

Mode of action

Allopurinol and its active metabolite, oxipurinol, inhibit xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine and xanthine to uric acid. Allopurinol also facilitates the incorporation of hypoxanthine and xanthine into DNA and RNA, further reducing serum uric acid concentrations. The drug has no anti-inflammatory, analgesic, or uricosuric actions.

Route of administration/doses

The adult oral dose is 100–900 mg daily, adjusted according to the serum uric acid level. The serum urate levels begin to decrease 24–48 hours after the initiation of treatment; the maximum effect is observed after 1–3 weeks.

Toxicity/side effects

A skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions, as well as Stevens–Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity, and rarely death.

Kinetics

Absorption

Allopurinol is well absorbed when administered orally; the bioavailability by this route is 80–90%.

Distribution

The drug is not protein-bound in the plasma; the V_D is 0.6 l/kg.

Metabolism

Allopurinol is rapidly converted to an active metabolite, oxipurinol.

Excretion

Occurs predominantly in the urine for both allopurinol and oxipurinol; some 20% is excreted in faeces. The clearance of allopurinol is 680 ml/min/kg and the elimination half-life is 1–3 hours.

Special points

An adequate urine output should be ensured during treatment with the drug; the dose of allopurinol should be reduced in the presence of severe renal impairment.

Allopurinol may protect against stress-induced, gastric mucosal injury by scavenging oxygen-derived free radicals.

The drug and its metabolites are removed by haemodialysis.

Amiloride

Uses

Amiloride is used in the treatment of:

1. oedema of cardiac, renal, or hepatic origin
2. hypertension and
3. in combination with loop or thiazide diuretics to conserve potassium.

Chemical

A pyrazinoylguanidine.

Presentation

As 5 mg tablets of amiloride hydrochloride and in various fixed dose combinations with thiazide or loop diuretics.

Main action

Diuretic.

Mode of action

Amiloride selectively blocks sodium reabsorption in the distal convoluted tubule. As a result of the inhibition of sodium ion transport, the electrical potential across the tubular epithelium decreases and potassium ion excretion is inhibited. The net result is a slight increase in renal sodium ion excretion and a decrease in excessive potassium ion excretion. Amiloride has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone.

Route of administration/doses

The adult oral dose is 10–20 mg daily. The diuretic effect commences within 2 hours and lasts 24 hours.

Effects

CVS

With chronic use, amiloride causes a slight decrease in the systolic and diastolic blood pressure, probably due to a reduction in the sodium ion content of arteriolar smooth muscle, producing a decrease in the systemic vascular resistance.

GU

The principal effect is diuresis, with an increased rate of sodium and bicarbonate ion excretion and a decreased rate of potassium, calcium, ammonium, and hydrogen ion excretion. The drug has no effect on free water clearance.

Metabolic/other

The inhibition of hydrogen ion excretion leads to a slight alkalinization of the urine; serum uric acid concentrations are also increased following the administration of amiloride. A metabolic acidosis may occur.

Toxicity/side effects

The most significant side effect of the drug is hyperkalaemia; other reported side effects, although rare, occur infrequently. These include nausea and vomiting, abdominal pain, diarrhoea, rashes, cramps, central nervous system and haemopoietic disturbances, impotence, and interstitial nephritis.

Kinetics

Absorption

Amiloride is incompletely absorbed when administered orally; the bioavailability by this route is 50%.

Distribution

The drug is 5% protein-bound in the plasma; the V_D is 5 l/kg.

Metabolism

No metabolism of the drug occurs in man.

Excretion

50% of the dose is excreted unchanged in the urine, the remainder in faeces. The clearance is 264–372 ml/min and the elimination half-life is 18–24 hours (this is prolonged to 140 hours in the presence of renal failure).

Special points

Amiloride inhibits the excretion of co-administered digoxin; concurrent NSAID therapy tends to obtund the diuretic and antihypertensive effects of the drug.

Aminoglycosides

Uses

Aminoglycosides are used in the treatment of infections of:

1. the respiratory tract
2. the urinary tract
3. skin and soft tissues
4. ocular infections
5. intra-abdominal sepsis
6. septicaemia
7. neutropaenic sepsis
8. severe neonatal infections
9. CNS sepsis
10. surgical prophylaxis.

Chemical

Aminocyclitol ring derivatives bound to amino sugars.

Presentation

Aminoglycosides in clinical use include gentamicin, amikacin, streptomycin, and neomycin. Gentamicin is available in a liquid form for topical use (ear/eye drops), in an intravenous form, and in a form suitable for intrathecal or intraventricular administration. Amikacin is available for intravenous use only. Neomycin is available in topical formulations combined with steroid (eye/ear/nasal drops; creams/ointments) or in tablet form. Streptomycin is available for intramuscular injection.

Main action

Aminoglycosides are active against:

1. Gram-positive bacteria (limited activity against *Streptococci species*)
2. Gram-negative bacteria.

These agents are not active against anaerobic bacteria. Acquired resistance is common due to plasmid translocation. Streptomycin is active against *Mycobacterium tuberculosis*. Neomycin is a bowel-sterilizing agent when administered orally.

Mode of action

Aminoglycosides bind irreversibly to specific bacterial ribosomal proteins (30S subunit) and inhibit protein synthesis by interfering with the initiation of the polypeptide chain and by inducing misreading of mRNA.

Route of administration/doses

Aminoglycosides may be administered topically as eye, ear, or nasal drops, as creams or ointments, orally (neomycin), intravenously, or via the intrathecal/intraventricular route. The specific dose, route, and frequency of an agent administered is dependent on the clinical indication, age of the patient, and the particular agent being used. Doses should be reduced in patients with renal impairment. Drug doses should be modified using drug level monitoring and trends in renal function.

Toxicity/side effects

Ototoxicity (with vestibular and auditory components) and nephrotoxicity (a form of acute tubular necrosis occurring 5–7 days after exposure) are the most serious side effects of the drug and both are correlated with high trough concentrations of aminoglycosides. Headaches, nausea and vomiting, rashes, and abnormalities of liver function tests have also been reported in association with the use of these agents.

Kinetics

Absorption

Aminoglycosides are not significantly absorbed when administered orally due to their low lipid solubility; approximately 3% of neomycin is absorbed. The drugs are not inactivated within the gastrointestinal tract.

Distribution

The V_D for gentamicin is 0.14–0.7 l/kg and that for amikacin is 0.34 l/kg. The percentage of drug bound to plasma proteins is 70–85% for gentamicin and <20% for amikacin. High concentrations are found within the renal cortex. The cerebrospinal fluid is poorly penetrated by these agents. Streptomycin penetrates tuberculous cavities well.

Metabolism

Aminoglycosides undergo minimal metabolism in man.

Excretion

Aminoglycosides are excreted unchanged almost completely by glomerular filtration. The clearance of gentamicin is 1.18–1.32 ml/kg/min and that of amikacin is 1.42 ml/kg/min. The half-life of gentamicin and amikacin is 2–3 hours (which markedly increases as renal function deteriorates).

Special points

Monitoring of drug levels of gentamicin and amikacin should follow local guidelines. Trough samples are taken immediately before a dose and peak levels an hour after drug administration. Gentamicin and amikacin are removed by haemofiltration and dialysis.

Direct administration of gentamicin into the cerebrospinal fluid via an indwelling extraventricular drain can by undertaken in the treatment of ventriculitis.

Neomycin has been used in the treatment of hepatic coma.

Aminoglycosides prolong the action of non-depolarizing muscle relaxants by inhibiting pre-synaptic acetylcholine release and stabilizing the post-synaptic membrane at the neuromuscular junction. This effect may be reversed by the administration of intravenous calcium. These agents should be used with caution in patients with myasthenia gravis.

Antimicrobial agents should always be administered following consideration of local pharmacy and microbiological policies.

Aminoglycosides exhibit synergy with other antibiotics, e.g. in the treatment of pneumonia and subacute bacterial endocarditis.

Aminophylline

Uses

Aminophylline is used in the treatment of:

1. asthma
2. chronic obstructive airways disease and
3. heart failure.

Chemical

The ethylenediamine salt of theophylline (a methylated xanthine derivative).

Presentation

As tablets containing 100/225/350 mg of aminophylline, as 180/360 mg suppositories, and as a clear solution for injection containing 25 mg/ml of aminophylline.

Main action

Bronchodilatation associated with an increased ventilatory response to hypoxia and hypercapnia. It has been shown to improve diaphragmatic contractility.

Mode of action

Aminophylline acts by inhibiting a magnesium-dependent phosphodiesterase, the enzyme responsible for the degradation of cAMP. The drug has a synergistic effect with those catecholamines which directly activate adenyl cyclase and lead to an increase in the intracellular concentration of cAMP. In addition, aminophylline interferes with the influx of calcium ions into smooth muscle cells and stabilizes mast cells by antagonizing the action of adenosine.

Route of administration/doses

The adult daily oral dose is 900 mg administered in 2–3 divided doses and the rectal dose 360 mg daily, titrated according to response. The loading dose by the intravenous route is 5 mg/kg over 10–15 minutes; this may be followed by a maintenance infusion of 0.5 mg/kg/hour. An intravenous loading dose should be administered with extreme caution to patients already receiving oral or rectal aminophylline. The therapeutic range is narrow (10–20 micrograms/ml) and estimations of the plasma concentration of aminophylline are valuable during chronic therapy.

Effects

CVS

The drug has mild positive inotropic and chronotropic effects, producing an increase in cardiac output and a decrease in systemic vascular resistance, thus leading to a decrease in arterial blood pressure. The left ventricular end-diastolic pressure and pulmonary capillary wedge pressure tend to decrease with the use of the drug. Aminophylline is arrhythmogenic at the upper extremes of its therapeutic range; it is synergistic with halothane in this respect.

RS

Aminophylline causes bronchodilatation, leading to an increase in vital capacity. It also increases the sensitivity of the respiratory centre to CO_2 and increases diaphragmatic contractility. Intravenous administration of the drug inhibits hypoxic pulmonary vasoconstriction and necessitates the administration of oxygen during therapy.

GU

Aminophylline increases the renal blood flow and glomerular filtration rate and decreases renal tubular sodium absorption, leading to a diuretic effect.

Metabolic/other

Hypokalaemia may occur secondary to the diuretic effect and also to increased cellular uptake of potassium. Abnormalities of liver function tests and inappropriate antidiuretic hormone secretion are also recognized effects of the drug.

Toxicity/side effects

Gastrointestinal and central nervous system disturbances (including convulsions after rapid intravenous administration) and cardiac dysrhythmias (including ventricular fibrillation) may occur, especially with plasma concentrations in excess of 20 micrograms/ml.

Kinetics

Absorption

Aminophylline is rapidly absorbed when administered orally and has a bioavailability by this route of 88–96%. Rectal absorption is slow and erratic.

Distribution

The drug is 50–60% protein-bound in the plasma; the V_D is 0.4–0.5 l/kg.

Metabolism

Occurs in the liver by demethylation and oxidation; a 3-methyl xanthine derivative is active.

Excretion

Demethylated metabolites are excreted in the urine; 10–13% of the dose is excreted unchanged. The clearance is 0.83–1.16 ml/min/kg; this is decreased in the presence of heart failure, liver disease, and in the elderly. Saturation of the metabolic pathways occurs near the therapeutic range; whilst obeying zero-order kinetics, the elimination half-life varies with the dose. Under conditions of first-order kinetics, the elimination half-life is 8 hours.

Special points

Co-administration of cimetidine, propranolol, or erythromycin will elevate plasma concentrations of aminophylline; conversely, co-administration of barbiturates, alcohol, or phenytoin will decrease plasma concentrations of aminophylline. The site of these interactions is at cytochrome P450. In high concentrations, the drug will antagonize non-depolarizing neuromuscular blockade.

Aminophylline infusion shortens the recovery time from enflurane–nitrous oxide anaesthesia.

Amiodarone

Uses

Amiodarone is used in the treatment of:

1. tachydysrhythmias inappropriate for or resistant to other drugs and
2. those associated with the Wolff–Parkinson–White syndrome.

Chemical

An iodinated benzofuran derivative.

Presentation

As 100/200 mg tablets of amiodarone hydrochloride and in ampoules and prefilled syringes containing 30/50 mg/ml of amiodarone hydrochloride for injection.

Main action

A class III antiarrhythmic agent.

Mode of action

Amiodarone acts by partial antagonism of alpha- and beta-agonists by reducing the number of receptors or by inhibiting the coupling of receptors to the regulatory subunit of the adenylate cyclase system. In addition, the drug has a direct action in isolated myocardial preparations to decrease the delayed slow outward potassium current and, in higher doses, additionally depresses the fast and slow inward currents which are due to sodium and calcium, respectively.

Route of administration/doses

The initial intravenous dose is 5 mg/kg, administered by infusion diluted in 250 ml of 5% glucose over 20–120 minutes via a central vein (the drug carrier is highly irritant). Most patients respond to an intravenous loading dose within 1 hour. Subsequently, 15 mg/kg/day may be administered intravenously if oral administration is not desirable or feasible. The adult oral dose is initially 200 mg 8-hourly, reducing to 100–200 mg daily after 1 week. The therapeutic level is 0.1 micrograms/ml.

Effects

CVS

Sinus rhythm is slowed by 15%, secondary to a reduction in the slow diastolic depolarization in nodal cells after the administration of amiodarone. Atrio-ventricular nodal automaticity is depressed and atrio- ventricular nodal conduction is slowed by 25% in the face of atrial tachycardia due to a decreased speed of depolarization of cells and an increase in the duration of the action potential. Amiodarone has no effect on conduction in the His bundle or ventricular myocardium. After oral administration, little effect is seen on the blood pressure or left ventricular contractility; the systemic vascular resistance decreases and coronary sinus blood flow increases. After intravenous administration, left ventricular contractility may decrease; the effects are otherwise similar to those observed after oral administration.

Metabolic/other

Abnormalities of liver function tests occur in up to 50% of patients; abnormalities of thyroid function tests may also occur due to inhibition of triiodothyronine and enhancement of reverse triiodothyronine production.

Toxicity/side effects

Almost all patients receiving amiodarone develop corneal microdeposits and one third develop signs of central nervous system toxicity. Pneumonitis, cirrhosis, peripheral neuropathy, photosensitivity, and gastrointestinal upsets are well recognized complications. Hypotension, cardiovascular collapse, and atrio-ventricular block have been reported after intravenous injection. Other dysrhythmias may arise, especially in the presence of hypokalaemia.

Kinetics

Absorption

The drug is incompletely absorbed after oral administration and has a bioavailability of 22–86%.

Distribution

Amiodarone is 96–98% protein-bound in the plasma; the V_D is 1.3–65.8 l/kg according to the dose.

Metabolism

The metabolic pathways of amiodarone have not been fully elucidated; it appears to be extensively metabolized in the liver, the major metabolite being desethyl-amiodarone which has antiarrhythmic properties and is cumulative.

Excretion

1–5% of the dose appears in the urine; the drug appears to be extensively excreted in the bile and faeces. The clearance is 0.14–0.6 l/min and the elimination half-life has been estimated at 4 hours to 52 days, depending on the dose and route of administration.

Special points

Modification of the dose is not required in the presence of renal impairment; amiodarone is not removed by haemodialysis. The actions of digoxin, calcium antagonists, oral anticoagulants, and beta-adrenergic antagonists may be potentiated by amiodarone due to displacement from plasma proteins. Bradycardia, complete and atrio-ventricular heart block resistant to atropine, adrenaline, and noradrenaline have been reported in patients receiving amiodarone undergoing general anaesthesia; it has been suggested that such patients may require temporary pacing in the perioperative period.

The drug is contraindicated in porphyria.

Amitriptyline

Uses

Amitriptyline is used for the treatment of:

1. depression
2. nocturnal enuresis and
3. can be used as an adjunct in the treatment of chronic pain syndromes, including chronic tension headache, post-herpetic neuralgia, painful neuropathies, and chronic spinal syndromes.

Chemical

A dibenzocycloheptadiene derivative.

Presentation

As tablets containing 10/25/50 mg and a clear, colourless solution for injection containing 10 mg/ml of amitriptyline hydrochloride. A syrup containing 2 mg/ml of amitriptyline embonate is also available.

Main actions

Antidepressant, sedative, and analgesic.

Mode of action

Tricyclic antidepressants potentiate the action of biogenic amines within the central nervous system by inhibiting the pre-synaptic reuptake of noradrenaline and serotonin. They also antagonize muscarinic cholinergic, alpha-1 adrenergic, and H1 and H2 histaminergic receptors.

Route of administration/doses

The adult oral dose is initially 75–150 mg/day, decreasing to 50–100 mg/day for maintenance. The corresponding parenteral dose is 10–20 mg 6-hourly. The drug takes from 3–30 days to become fully effective.

Effects

CVS

In high doses, amitriptyline may cause postural hypotension, tachycardia, dysrhythmias, and an increase in the conduction time through the atrio-ventricular node.

RS

The drug may cause respiratory depression when administered in toxic doses.

CNS

The predominant effect of the drug is an antidepressant action which may take several weeks to develop; sedation, weakness, and fatigue are also commonly produced.

Toxicity/side effects

A wide spectrum of cardiovascular, central nervous system, gastrointestinal, and haematological disturbances may complicate the use of amitriptyline. Anticholinergic side effects (blurred vision, dryness of the mouth, constipation, and urinary retention) tend to predominate.

Kinetics

Absorption

The drug is rapidly absorbed when administered orally; the bioavailability is 45% by this route.

Distribution

Amitriptyline is 95% protein-bound in the plasma; the V_D is 18–22 l/kg.

Metabolism

Occurs by N-demethylation and hydroxylation with subsequent conjugation to glucuronide and sulphate. Nortriptyline is an intermediate active metabolite.

Excretion

The conjugates are excreted in the urine. The clearance is 9.7–15.3 ml/min/kg and the elimination half-life is 12.9–36.1 hours.

Special points

Scopolamine and the phenothiazines displace tricyclic antidepressants from their binding sites on plasma proteins and thus increase the activity of the latter; barbiturates increase the rate of hepatic metabolism of tricyclic antidepressants and decrease their activity. Amitriptyline accentuates the cardiovascular effects of adrenaline; care should be exercised when local anaesthetic agents containing adrenaline are used in patients receiving the drug. Amitriptyline also increases the likelihood of dysrhythmias and hypotension occurring during general anaesthesia.

Amoxicillin

Uses

Amoxicillin is used in the treatment of:

1. ear, nose and throat, and respiratory tract infections
2. urinary tract infections, including gonorrhoea
3. septicaemia
4. gastroenteritis
5. endocarditis and
6. meningitis.



Chemical

An aminopenicillin derivative of ampicillin.

Presentation

Amoxicillin is available in the following formulations:

1. in vials containing 250/500/1000 mg of amoxicillin sodium
2. in sachets containing 3 g of amoxicillin trihydrate for reconstitution
3. in capsules containing 250/500 mg of amoxicillin trihydrate

4. as a suspension containing 125 mg of amoxicillin trihydrate per 1.25 ml
5. as a syrup containing 125 mg/5 ml and 250 mg/5 ml of amoxicillin trihydrate.

The drug is also available in a variety of formulations in combination with the beta-lactamase inhibitor, clavulanic acid, as co-amoxiclav.

Main actions

Amoxicillin is bactericidal against a wide range of organisms, including some strains of the Gram-negative *Haemophilus influenzae* and *Escherichia coli* (benzylpenicillin showing lower activity against these species), *Proteus mirabilis*, *Bordetella pertussis*, and *Neisseria*, *Salmonella*, and *Shigella* spp. The drug is nearly always effective against the Gram-positive *Streptococcus* and *Clostridium* spp. (not *Clostridium difficile*). 90% of staphylococci are resistant. It is ineffective against *Pseudomonas* and *Klebsiella* spp. and penicillinase-producing organisms. The addition of clavulanic acid reduces the minimum inhibitory concentration against the following organisms: *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, and *Klebsiella* spp.

Mode of action

Amoxicillin acts in the manner typical of penicillins; it binds to penicillin-binding proteins in the bacterial cell wall and inhibits pentapeptide cross-linking during its formation, resulting in cell wall disruption.

Routes of administration/doses

The adult oral dose is 250–500 mg 8-hourly and the corresponding parenteral dose is 500 mg 8-hourly, increased to 1 g 6-hourly in severe infections. Drug dosage and frequency may be modified on an individual patient basis in the treatment of severe infections.

Toxicity/side effects

Allergic phenomena, gastrointestinal upsets, interstitial nephritis, and haemopoietic disturbances may complicate the use of the drug. Amoxicillin and clavulanic acid use are associated with the late development of cholestatic jaundice.

Kinetics

Absorption

The drug is rapidly absorbed when administered orally; the bioavailability by this route is 72–94%. The bioavailability of clavulanic acid is approximately 60% although it exhibits marked variability between individuals.

Distribution

Amoxicillin is 17–20% protein-bound in the plasma, predominantly to albumin; the V_D is 0.3–0.4 l/kg. Clavulanic acid is 22% protein- bound; the V_D is 0.2 l/kg.

Metabolism

30% is metabolized in the liver. Clavulanic acid undergoes 50–70% hepatic metabolism.

Excretion

The clearance of amoxicillin is 250–370 ml/min and the elimination half-life is 61.3 minutes. 40% of clavulanic acid undergoes renal elimination (18–35% as unchanged drug). It has a clearance of 260 ml/min and an elimination half-life of approximately 1 hour.

Special points

A reduced dosing frequency should be considered in patients with severe renal impairment. Both amoxicillin and clavulanic acid are removed by haemodialysis.

Amphotericin

Uses

Amphotericin is used in the treatment of life-threatening systemic fungal infections, especially disseminated candidosis, coccidiomycosis, histoplasmosis, aspergillosis, and cryptococcosis. Amphotericin may also be administered orally for selective decontamination of the gut.

Chemical

Amphotericin is a mixture of two polyene macrolides (amphotericin A and B) produced by *Streptomyces nodosus*.

Presentation

As 100 mg tablets and a yellow powder in vials containing 50 000 units of amphotericin (with sodium desoxycholate which solubilizes amphotericin); the mixture forms a colloidal suspension in water; as a yellow opaque suspension of 5 mg/ml of amphotericin B complexed with two phospholipids in a 1:1 drug to lipid molar ratio with a ribbon-like structure, pH 5–7; as liposomal amphotericin, a lyophilized 50 mg product presentation where the 100 nm liposomes are created so that the amphotericin is intercalated within the unilamellar bilayer structure; as an elongated disc structure, 100 nm in diameter, in a 1:1 molar ratio of amphotericin B and cholesteryl sulphate in 50 and 100 mg vials, presented in lyophilized powder for reconstitution to form a colloidal dispersion.

Main actions

Amphotericin is a fungistatic antibiotic which is active against a wide range of yeasts and yeast-like fungi, including *Candida albicans*.

Mode of action

The drug binds to cell membrane sterols, leading to altered membrane permeability to univalent ions, water, and small non-electrolyte molecules. Leakage of intracellular components occurs, cell growth is inhibited, and cell death may result. Amphotericin binds preferentially to sterols (especially ergosterol) in fungal cell membranes, although it does bind to sterols (especially cholesterol) in animal cell membranes where it exerts similar effects.

Route of administration/doses

Amphotericin is administered by slow intravenous infusion (via a dedicated vein) diluted in 5% glucose over 6 hours; the daily dose is 0.25–1.5 mg/kg and treatment will usually be required for a period of several weeks. Intrathecal, topical, and nebulized administration of the drug have also been described.

Effects

GU

Deterioration of renal function leading to hypokalaemia, renal tubular acidosis, or nephrocalcinosis occurs in more than 80% of patients who receive the drug; this is usually reversible, but may need renal replacement therapy.

Metabolic/other

The drug may decrease serum magnesium levels. Amphotericin may alter immune function (especially that of T cells and monocytes) and thereby, potentiate host defences.

Toxicity/side effects

The list of side effects reported with the use of amphotericin is lengthy. Gastrointestinal upsets (anorexia, nausea and vomiting, loss of weight), haematological impairment (anaemia, thrombocytopaenia, leucopaenia), and disturbances of the central nervous system (headache, muscle pains, vision disturbances, hearing loss, convulsions, peripheral neuropathy) may occur. The drug may also cause fever and phlebitis; acute dysrhythmias have also been reported.

Kinetics

The assay only distinguishes amphotericin B.

Absorption

The drug is poorly absorbed when administered orally.

Distribution

Amphotericin is 90–95% bound in the plasma to lipoproteins; the V_D is 3.6–4.4 l/kg.

Metabolism

The metabolic pathway of amphotericin has not been established; the liver appears to be the principal site of metabolism.

Excretion

The drug is predominantly excreted in the urine, 2–5% unchanged. The dose should be reduced in the presence of renal impairment as continued use of the drug may lead to further renal impairment. The clearance is 0.35– 0.51 ml/min/kg and the elimination half-life is 15 days. The high clearance and large V_D indicate tissue uptake and the long half-life indicates slow redistribution from tissues. Non-linear behaviour occurs with increasing dosage.

Special points

Liposomal encapsulation or incorporation into a lipid complex can substantially affect the action of amphotericin compared to the free drug. There is a theoretical risk of amphotericin enhancing the effect of non-depolarizing relaxants and digoxin secondary to the hypokalaemia that the former produces. Liposomal amphotericin (amphotericin incorporated into unilamellar liposomes) is safe, effective, and better tolerated, but may cause disordered liver function tests. The drug is poorly dialysable.

Aspirin

Uses

Aspirin is used:

1. for the treatment of pain of mild to moderate severity and severe bone pain
2. as an anti-inflammatory agent, e.g. in rheumatoid arthritis and osteoarthritis
3. as an antipyretic
4. for the prevention of recurrence after myocardial infarction
5. for the prevention of graft occlusion after coronary artery surgery
6. in the treatment of pre-eclampsia
7. for the prevention of transient ischaemic attacks and
8. DVT prophylaxis post-fractured neck of femur.



Chemical

An aromatic ester of acetic acid.

Presentation

As 75/100/300/600 mg tablets of aspirin and in a variety of fixed dose combinations.

Main actions

Antipyretic, analgesic, and anti-inflammatory.

Mode of action

Aspirin acetylates and thereby inhibits the enzyme cyclo-oxygenase which converts arachidonic acid to cyclic endoperoxides, thus preventing the formation of prostaglandins and thromboxanes. Prostaglandins are involved in the sensitization of peripheral pain receptors to noxious stimuli. It may also inhibit the lipo-oxygenase pathway by an action on hydroperoxy fatty acid peroxidase. The drug inhibits cyclo-oxygenase irreversibly in platelets, but not in the endothelium.

Route of administration/doses

The adult oral dose is 300–900 mg, 6–8-hourly; aspirin is not recommended for use in children under 12 years of age.

Effects

CVS

Aspirin has minimal haemodynamic effects at normal doses; however, platelet aggregation is inhibited and bleeding time is increased by a decrease in thromboxane A2 production (with large doses, the concentration of prothrombin is decreased).

RS

Therapeutic doses of aspirin increase oxygen consumption and carbon dioxide production by uncoupling oxidative phosphorylation. Overdosage may lead to hyperventilation (by a direct action of the drug on the respiratory centre), pulmonary oedema, and respiratory failure.

CNS

The analgesic effect of the drug appears to be exerted by both central and peripheral mechanisms; the antipyretic effect may be a manifestation of inhibition of prostaglandin synthesis at the hypothalamic level.

AS

Aspirin increases gastric acid production.

GU

The drug may cause proteinuria and an increase in the number of renal tubular casts appearing in the urine. Aspirin is uricosuric in high doses, but paradoxically decreases urate excretion at low doses.

Metabolic/other

Blood sugar tends to decrease with low doses and increase with high doses of aspirin. Transient elevation of serum urea concentrations and elevation of liver enzymes may occur. Lipogenesis is decreased; very large doses of aspirin stimulate steroid secretion.

Toxicity/side effects

Gastrointestinal upsets occur in 2–6%; haemorrhage and gastric ulceration occur in about 1 in 10 000 of habitual users of aspirin. Large doses of the drug taken over a prolonged period may cause hepatic impairment and renal papillary necrosis, leading to chronic renal failure. Allergic response (including bronchospasm), central nervous system disturbances, and aplastic anaemia may also occur. The use of aspirin is associated with the development of Reye's syndrome in children.

Kinetics

Absorption

Aspirin is rapidly and completely absorbed from the upper gastrointestinal tract and has a bioavailability of 70% due to an extensive first-pass metabolism.

Distribution

Aspirin is rapidly hydrolyzed to salicylic acid; the pharmacokinetics are of this compound. Salicylic acid is 80–90% protein-bound in the plasma, primarily to albumin. The V_D is 9.6–12.71. The drug has only a limited ability to cross the blood–brain barrier.

Metabolism/excretion

At therapeutic doses, 50% of salicylic acid is metabolized to salicylurate in the liver via a saturable enzyme pathway. A further 20% is metabolized to salicylphenolic glucuronide which is also a saturable pathway. First-order kinetics occurs with the metabolic pathways of salicylacyl glucuronide (10%) and gentisic acid (5%) production and with the urinary excretion of salicylic acid (15%). Due to the two saturable metabolic pathways, the elimination of salicylic acid obeys non-linear kinetics, i.e. the half-life varies with the dose administered.

Special points

Salicylates may increase the effect of co-administered oral anticoagulants and sulphonylureas due to displacement from plasma proteins.

Overdosage with aspirin has a mortality of 1–2% and may result in respiratory alkalosis or metabolic acidosis according to the age of the patient and the time of ingestion. Alkalization of the urine increases the excretion of free salicylic acid; the fraction of free drug may increase from 5 to 85%. This principle is used in forced alkaline diuresis and aspirin is removed by haemodialysis. A normal bleeding time should be demonstrated before embarking upon spinal or epidural anaesthesia in patients receiving aspirin.

Preoperative ingestion of aspirin is associated with increased blood loss during open heart surgery and prostatectomy.

Atenolol

Uses

Atenolol is used in the treatment of:

1. hypertension
2. angina
3. tachydysrhythmias and
4. in the acute phase of myocardial infarction and prevention of reinfarction.

Chemical

A phenoxypropanolamine.

Presentation

As 25/50/100 mg tablets (and in fixed dose combinations with nifedipine, amiloride, and chlorthalidone), a 0.5% syrup, and as a clear, colourless solution for injection containing 0.5 mg/ml of atenolol.

Main action

Atenolol is negatively inotropic and chronotropic, leading to a fall in myocardial oxygen consumption; it also has antihypertensive and antiarrhythmic properties.

Mode of action

Atenolol acts by reversible, competitive blockade of cardiac beta-1 receptors and also has some action at beta-2 receptors.

Route of administration/doses

The adult oral dose is 50–100 mg daily. Intravenously, 2.5–10 mg may be administered at a rate of 1 mg/min until the desired effect is achieved.

Effects

CVS

Sinus node automaticity and atrio-ventricular nodal conduction are decreased. The effective refractory periods of the atrial and atrio-ventricular nodes are all increased by the administration of atenolol. No effect is seen on conduction in the His–Purkinje system or the effective refractory period of the ventricles. The ensuing negative inotropic and chronotropic effects lead to a decrease in myocardial oxygen consumption. Atenolol has no intrinsic sympathomimetic activity. The drug has a prolonged antihypertensive effect and can lead to regression of left ventricular hypertrophy in hypertensive patients.

RS

Little effect is seen on lung function due to the cardioselectivity of atenolol.

CNS

Poor central nervous system penetration means that little effect is seen; however, sleep disturbances and vivid dreams have been reported.

GU

A clinically insignificant elevation in serum urea or creatinine may be produced by the drug.

Metabolic/other

The plasma triglyceride levels may increase and HDL cholesterol levels may decrease following the use of atenolol.

Toxicity/side effects

The side effects are predictable manifestations of the pharmacological effects of the drug: exacerbation of peripheral vascular disease, bronchospasm, masking of the signs of hypoglycaemia, depression, impotence, and altered bowel habit. The precipitation of heart failure by atenolol is rare.

Kinetics

Absorption

The oral bioavailability is 50%.

Distribution

Atenolol is 3% protein-bound in the plasma; the V_D is 0.7 l/kg.

Metabolism

Less than 10% is metabolized in the liver.

Excretion

The drug is excreted largely unchanged in the urine. The clearance is 77 ml/min/kg (which is decreased in the presence of renal failure) and the elimination half-life is 6–9 hours.

Special points

The dosage should be reduced in renal failure if the glomerular filtration is less than 35 ml/min; the drug is readily dialysable.

Beta-blockade should be continued throughout the perioperative period; a single preoperative dose of atenolol may be as valuable as chronic treatment in the anaesthetic management of patients with borderline hypertension and in decreasing the hypertensive response to intubation and subsequent dysrhythmias. Beta-blockade may improve perioperative mortality from cardiovascular events.

Atracurium

Uses

Atracurium is used to facilitate intubation and controlled ventilation.

Chemical

A benzyl isoquinolinium ester which is a mixture of ten stereoisomers due to the presence of four chiral centres.

Presentation

As a clear, colourless, or pale yellow solution for injection available in 2.5 ml, 5 ml, and 25 ml vials, containing 10 mg/ml of atracurium besilate (equivalent to atracurium 7.5 mg/ml), needing to be stored at 2–8°C. It has a pH of between 3.25 and 3.65.

Main action

Competitive, non-depolarizing neuromuscular blockade.

Mode of action

Atracurium acts by competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction.

Route of administration/doses

The drug is administered intravenously. The ED_{95} of atracurium is estimated to be 0.23 mg/kg. An initial dose of 0.3–0.6 mg/kg is recommended, providing muscle relaxation for between 15–35 minutes. Endotracheal intubation can be achieved within 90–120 seconds of an intravenous dose of 0.5–0.6 mg/kg with maximal resultant neuromuscular blockade achieved within 3–5 minutes following administration. 95% recovery of the twitch height occurs within approximately 35 minutes. Maintenance of neuromuscular blockade may be achieved with bolus doses of 0.1–0.2 mg/kg. Atracurium may be administered by intravenous infusion at a rate of 0.3–0.6 mg/kg/hour although there is wide inter-patient variability in dosage requirements, particularly in patients on ventilation in intensive care. Induced hypothermia to a temperature of approximately 25°C reduces the rate of metabolism of atracurium. Consequently, neuromuscular block can be maintained with approximately half the original infusion rate. The drug is non-cumulative with repeated or continuous administration. 95% recovery of twitch height, following a single dose of atracurium, occurs within 35 minutes.

Effects

CVS

Atracurium has minimal cardiovascular effects; there is a change of less than 5% in the heart rate, mean arterial pressure, systemic vascular resistance, central venous pressure, and pulmonary capillary wedge pressure following administration of the drug. The incidence of transient hypotension ranges from 1 to 14% in clinical trial data using doses of 0.3 mg/kg to 0.6 mg/kg or greater.

RS

Bronchospasm may occasionally occur secondary to histamine release in approximately 0.2% of patients.

CNS

The drug has no effect on intracranial or intraocular pressure.

AS

Lower oesophageal sphincter pressure is unaffected by administration of atracurium.

Toxicity/side effects

Histamine release may occur (by up to 92%) if doses greater than 0.6 mg/kg are used, leading to cutaneous flushing (2–3%), hypotension, and bronchospasm. Bradycardia has been reported following the administration of atracurium. There have been rare reports of fatal anaphylactoid reactions with the administration of atracurium. Cross-sensitivity may exist with vecuronium, rocuronium, and pancuronium. Administration of atracurium by intravenous infusion to critically ill patients on intensive care has been associated with the development of a critical illness neuropathy/myopathy.

Kinetics

Distribution

Atracurium is 82% protein-bound in the plasma; the V_D is 0.16–0.18 l/kg. The drug does not cross the blood–brain barrier. Atracurium does cross the placenta, but not in clinically significant amounts.

Metabolism

Occurs by two pathways; the major pathway is via Hofmann degradation (cleavage of the link between the quaternary nitrogen ion and the central chain) to laudanosine and a quaternary monoacrylate.

Laudanosine is cleared primarily by the liver. The minor degradative pathway is via hydrolysis by non-specific esterases in the blood to a quaternary alcohol and a quaternary acid. The metabolites have insignificant neuromuscular-blocking activity.

Excretion

The clearance is 5.1–6.1 ml/kg/min and the elimination half-life is 17–21 minutes; these parameters are little altered by renal or hepatic impairment and no alteration in dose is necessary in these patients.

Special points

The duration of action of atracurium, in common with other non-depolarizing relaxants, is prolonged by hypokalaemia, hypocalcaemia, hypermagnesaemia, hypoproteinaemia, dehydration, acidosis, and hypercapnia. The following drugs, when co-administered with atracurium, increase the effect of the latter: volatile anaesthetic agents (isoflurane increases the activity by up to 35%, induction agents (including ketamine), fentanyl, suxamethonium, diuretics, calcium channel blockers, alpha- and beta-adrenergic antagonists, protamine, lidocaine, metronidazole, and the aminoglycoside antibiotics. Patients with burns may develop resistance to the effect of atracurium. The onset of neuromuscular blockade is likely to be lengthened and the duration of action shortened in patients receiving chronic anticonvulsant therapy. The use of atracurium appears to

be safe in patients susceptible to malignant hyperpyrexia.

Laudanosine (in concentrations >17 micrograms/ml) has been shown to cause seizures in animal models and becomes measurable in patients who have received atracurium by infusion for 6 days; the clinical significance of this is unclear. Haemofiltration has a minimal effect on plasma levels of atracurium or laudanosine. The stereoisomer, cis-atracurium, causes less histamine release and is available commercially. Atracurium, due to its acidic pH, should not be mixed with alkaline solutions (e.g. barbiturates).

Atropine

Uses

Atropine is used:

1. traditionally to dry secretions prior to ether or chloroform anaesthesia (nowadays when a dry airway is desirable, especially in children under 1 year of age)
2. to counter bradycardia due to increased vagal tone
3. to counter the muscarinic effects of anticholinergic agents
4. during cardiopulmonary resuscitation
5. as a cycloplegic
6. as a constituent of cold cures and
7. in the treatment of organophosphorus poisoning and
8. tetanus.

Chemical

An alkaloid from *Atropa belladona*; atropine is a tertiary amine which is the ester of tropic acid and tropine. Commercial atropine is the racemic mixture of D- and l-hyoscyamine (l-form is active).

Presentation

As a clear, colourless solution for injection containing 0.5/0.6 mg/ml and 3 mg in 10 ml of atropine sulphate; it is also available as 0.6 mg tablets.

Main action

Anticholinergic.

Mode of action

Atropine exerts its effects by competitive antagonism of acetylcholine at muscarinic receptors (having little effect at nicotinic receptors except at high doses).

Route of administration/doses

Atropine may be administered intramuscularly or intravenously in a dose of 0.015–0.02 mg/kg. The adult oral dose is 0.2–0.6 mg. A total of 3 mg is needed for complete vagal blockade in adults.

Effects

CVS

In low doses, atropine may produce an initial bradycardia (Bezold–Jarisch reflex) followed by tachycardia (the usual effect). The cardiac output is increased, but there is little effect on blood pressure. Atropine decreases the atrio-ventricular conduction time and may produce dysrhythmias. Dilatation of facial capillaries may occur with the use of high doses.

RS

Atropine produces bronchodilation with an increase in physiological dead space. Bronchial secretions are reduced by the drug. The respiratory rate is increased and a decreased incidence of laryngospasm has been reported following the administration of the drug.

CNS

Central excitation or depression may occur (central anticholinergic syndrome). The syndrome is characterized by somnolence, confusion, amnesia, agitation, hallucinations, dysarthria, ataxia, or delirium. Atropine also has antiemetic and anti-Parkinsonian actions.

AS

The drug reduces salivation, the volume of gastric secretions, and tone and peristalsis throughout the gut. Atropine has a mild antispasmodic action on the biliary tree. The lower oesophageal tone is reduced by the drug.

GU

Tone and peristalsis in the urinary tract are decreased.

Metabolic/other

Cycloplegia, mydriasis, and an increase in intraocular pressure may be produced by the drug. Sweating is inhibited and the basal metabolic rate is increased. The drug suppresses ADH secretion. Atropine has local anaesthetic properties.

Toxicity/side effects

Atropine is painful when injected intramuscularly and the sensation of a dry mouth is unpleasant. The central anticholinergic syndrome may occur in the elderly and inhibition of sweating may lead to hyperpyrexia in children. Urinary retention may be precipitated by the drug. Glaucoma may result from ocular (but not intravenous or intramuscular) administration.

Kinetics

Absorption

Atropine is rapidly absorbed from the gut; the bioavailability by oral route is 10–25%.

Distribution

Atropine is 50% protein-bound in the plasma, the V_D is 2.0–4.0 l/kg. The drug crosses the placenta and blood–brain barrier.

Metabolism

Atropine is hydrolyzed in the liver and tissues to tropine and tropic acid.

Excretion

94% of the dose is excreted in the urine in 24 hours, some unchanged. The clearance is 70 l/hour and the elimination half-life is 2.5 hours.

Special points

Atropine reduces the incidence and morbidity of oculocardiac crises.







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Bendroflumethiazide

Uses

Bendroflumethiazide is used in the treatment of:

1. hypertension
2. oedema due to heart failure or the nephrotic syndrome
3. diabetes insipidus
4. renal tubular acidosis
5. hypercalciuria and
6. for the inhibition of lactation.

Chemical

A thiazide.

Presentation

As 2.5/5 mg tablets of bendroflumethiazide and in a variety of fixed dose combinations with beta-adrenergic antagonists.

Main actions

Diuretic and antihypertensive.

Mode of action

Thiazide diuretics inhibit sodium chloride co-transport in the distal convoluted tubule. They inhibit sodium ion reabsorption, which results in an increased urinary excretion of sodium, potassium, and water.

Route of administration/doses

The adult oral dose is 2.5–10 mg daily. Bendroflumethiazide has duration of action of 12–18 hours.

Effects

CVS

Bendroflumethiazide exerts its antihypertensive effect by decreasing the plasma volume and as a vasodilator. It also causes a slight decrease in the cardiac output.

CNS

In toxic doses, the drug causes depression of the central nervous system.

GU

Bendroflumethiazide decreases the renal blood flow and may also cause a reduction in the glomerular filtration rate. The drug decreases the urinary excretion of calcium and increases that of sodium, potassium, and magnesium.

Metabolic/other

Thiazide diuretics may increase the blood sugar concentration by enhancing glycogenolysis and decreasing the rate of glycogenesis and insulin secretion. They may also increase serum urate, triglyceride, and cholesterol concentrations and give rise to a hypochloraemic acidosis.

Toxicity/side effects

Central nervous system and haemopoietic disturbances, rashes, impotence, and acute pancreatitis may complicate the use of the drug. Bendroflumethiazide may interfere with diabetic control and produce hypercholesterolaemia and gout and it may aggravate renal or hepatic insufficiency.

Kinetics

Absorption

Bendroflumethiazide is completely absorbed when administered orally.

Distribution

Bendroflumethiazide is completely absorbed when administered orally.

Metabolism

The drug is 94% protein-bound in the plasma; the V_D is 1.18 l/kg.

Excretion

Occurs predominantly in the urine, 30% unchanged. The clearance is 3.68 ml/min/kg and the elimination half-life is 2.7–4.1 hours.

Special points

The drug may cause hypokalaemia and hypercalcaemia, which may precipitate digoxin toxicity, potentiate the effect of non- depolarizing muscle relaxants, and increase the likelihood of dysrhythmias occurring during general anaesthesia.

The hypotension occurring secondary to the administration of opioids, barbiturates, and halothane is reportedly exaggerated in patients receiving thiazide diuretics.

Bupivacaine

Uses

Bupivacaine is used as a local anaesthetic.

Chemical

An amide which is a structural homologue of mepivacaine.

Presentation

As a clear, colourless solution containing racemic bupivacaine (S- and R-enantiomers) in concentrations of 0.25% (2.64 mg/ml equivalent to bupivacaine hydrochloride anhydrous 2.5 mg/ml) and 0.5% (5.28 mg/ml equivalent to bupivacaine hydrochloride anhydrous 5.0 mg/ml). The 0.25/0.5% solutions are available combined with 1:200,000 adrenaline, which contain the preservative, sodium metabisulphite. A 0.5% (‘hyperbaric’ or ‘heavy’) solution containing 80 mg/ml of glucose (with a specific gravity of 1.026) is also available. 0.1% bupivacaine is available as a mixture with 2 micrograms/ml fentanyl for epidural use. The S-enantiomer is available as levobupivacaine hydrochloride in the following concentrations: 2.5 mg/ml, 5 mg/ml, and 7.5 mg/ml. Levobupivacaine is also available for epidural use in the following concentrations: 0.625 mg/ml and 1.25 mg/ml. The pKa of bupivacaine is 8.1 and is 15% unionized at a pH of 7.4. The heptane:buffer partition coefficient is 27.5.

Main action

Local anaesthetic.

Mode of action

Local anaesthetics diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels; here they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channels, thereby decreasing sodium ion conductance and preventing the depolarization of the cell membrane.

Routes of administration/doses

Bupivacaine may be administered topically, by infiltration, intrathecally, or epidurally; the toxic dose of bupivacaine is 2 mg/kg (with or without adrenaline). The maximum dose is 150 mg. The drug acts within 10–20 minutes and has duration of action of 5–16 hours.

Effects

CVS

Bupivacaine is markedly cardiotoxic; it binds specifically to myocardial proteins in addition to blocking cardiac sodium channels and decreasing the rate of increase of phase 0 during the cardiac action potential. In toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility, producing hypotension and possibly cardiovascular collapse. Potassium and calcium ion channels may also be affected at toxic doses. Levobupivacaine-induced cardiotoxicity requires a greater dose to be administered compared with racemic bupivacaine.

CNS

The principle effect of bupivacaine is reversible neural blockade; this leads to a characteristically biphasic effect in the central nervous system. Initially, excitation

(lightheadedness, dizziness, visual and auditory disturbances, and seizure activity) occurs due to inhibition of inhibitory interneuron pathways in the cortex. With increasing doses, depression of both facilitatory and inhibitory pathways occurs, leading to central nervous system depression (drowsiness, disorientation, and coma). Local anaesthetic agents block neuromuscular transmission when administered intraneurally; it is thought that a complex of neurotransmitter, receptor, and local anaesthetic is formed which has negligible conductance.

Levobupivacaine produces less motor blockade, but longer sensory blockade following epidural administration.

Toxicity/side effects

Allergic reactions to the amide-type local anaesthetic agents are extremely rare. The side effects are predominantly correlated with excessive plasma concentrations of the drug, as described above. The use of the drug for intravenous regional blockade is no longer recommended as refractory cardiac depression, leading to death, has been reported when it is used for this purpose.

Kinetics

Absorption

The absorption of local anaesthetic agents is related to:

1. the site of injection (intercostal > caudal > epidural > brachial plexus > subcutaneous)
2. the dose—a linear relationship exists between the total dose and the peak blood concentrations achieved and
3. the presence of vasoconstrictors which delay absorption.

The addition of adrenaline to bupivacaine solutions does not influence the rate of systemic absorption as:

1. the drug is highly lipid-soluble and therefore, its uptake into fat is rapid and
2. the drug has a direct vasodilatory effect.

Distribution

Bupivacaine is 95% protein-bound in the plasma to albumin and alpha-1 acid glycoprotein; the V_D is 21–103 l. An *in vitro* study of levobupivacaine protein-binding in man demonstrated plasma protein binding to be >97% at concentrations between 0.1 and 1.0 micrograms/ml.

Metabolism

Occurs in the liver by N-dealkylation, primarily to pipecolylxylidine. N-desbutyl bupivacaine and 4-hydroxy bupivacaine are also formed. There is no evidence of *in vivo* racemization of levobupivacaine. *In vitro* studies of levobupivacaine demonstrate that CYP3A4 and CYP1A2 are responsible for its metabolism to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively.

Excretion

5% of the dose is excreted in the urine as pipecolylxylidine; 16% is excreted unchanged. The clearance is 0.47 l/min and the elimination half-life (after intravenous administration) is 0.31–0.61 hours.

Special points

The onset and duration of conduction blockade is related to the pKa, lipid solubility, and the extent of protein binding. A low pKa and high lipid solubility are associated with a rapid onset time; a high degree of protein binding is associated with a long duration of action. In infants under 6 months of age, the low level of albumin and alpha-1 acid glycoprotein results in an increase in the free fraction of bupivacaine. Local anaesthetic agents significantly increase the duration of action of both depolarizing and non-depolarizing relaxants. Levobupivacaine may precipitate if diluted in alkaline solutions. Clonidine (8.4 micrograms/ml), morphine (0.05 mg/ml), and fentanyl (4 micrograms/ml) have been shown to be compatible with levobupivacaine.

Buprenorphine

Uses

Buprenorphine is used:

1. in the treatment of moderate to severe pain and has been used
2. in sequential analgesia.

Chemical

A synthetic derivative of the alkaloid thebaine.

Presentation

As a clear, colourless solution containing 300 micrograms/ml buprenorphine hydrochloride, 200/400 micrograms tablets and

various strengths of transdermal patches.

Main actions

Analgesia.

Mode of action

The mode of action of buprenorphine remains to be fully elucidated. The drug acts as a partial agonist at mu-opioid receptors, but dissociates slowly from the latter, leading to prolonged analgesia. Buprenorphine appears also to have a high affinity for (but a low intrinsic activity at) kappa-opioid receptors. One unusual property of buprenorphine hydrochloride observed *in vitro* is its very slow rate of dissociation from its receptor. This may explain its longer duration of action than morphine, the unpredictability of its reversal by opioid antagonists, and its low level of manifest physical dependence.

Route of administration/doses

The adult intramuscular and intravenous dose is 0.3–0.6 mg 6–8-hourly; the corresponding sublingual dose is 0.2–0.4 mg 6–8-hourly. The drug is also effective when administered by the epidural route; a dose of 0.3 mg has been recommended. The dose for transdermal delivery should be evaluated after 24–72 hours and adjusted according to instructions due to the slow rise in plasma levels. Buprenorphine has a significantly longer latency period and duration of action than morphine.

Effects

CVS

Buprenorphine has minimal cardiovascular effects; the heart rate may decrease (by up to 25%) and the systolic blood pressure may fall by 10% following administration of the drug.

RS

The drug produces respiratory depression and an antitussive effect, similar to that produced by morphine. Buprenorphine may cause histamine and tryptase release from lung parenchymal mast cells and may increase pulmonary vascular resistance.

CNS

The drug is 25 times as potent an analgesic as morphine. In common with other opioids, buprenorphine produces miosis. The drug decreases cerebral glucose metabolism by up to 30%.

GU

The drug has been shown to reduce the rate of urine output in animals.

Metabolic/other

Buprenorphine decreases the release of luteinizing hormone and increases the release of prolactin.

Toxicity/side effects

Side effects are similar in nature and incidence to those produced by morphine. Drowsiness, dizziness, headache, confusion, dysphoria, and nausea and vomiting may be produced by the drug. Buprenorphine appears to be less liable to produce dependence than pure mu-agonists.

Kinetics

Absorption

The drug is absorbed when administered orally, but undergoes a significant first-pass metabolism and the sublingual route is therefore preferred. The bioavailability is 40–90% when administered intramuscularly and 44–94% when administered sublingually.

Distribution

Only unchanged buprenorphine appears to reach the central nervous system. The drug is 96% protein-bound *in vitro*; the V_D is 3.2 l/kg.

Metabolism

Occurs in the liver by dealkylation with subsequent conjugation to glucuronide; the polar conjugates then appear to be excreted in the bile and hydrolyzed by bacteria in the gastrointestinal tract.

Excretion

Occurs predominantly via the faeces as unchanged buprenorphine; the remainder is excreted in the urine as conjugated buprenorphine and dealkylated derivatives. The clearance is 934 ml/min (this is decreased by 30% under general anaesthesia) and the elimination half-life is 5 hours.

Special points

Being a partial agonist, buprenorphine antagonizes the effects of morphine and other opioid agonists and may precipitate abstinence syndromes in opiate-dependent subjects. The respiratory depressant effects of the drug are not completely reversed by even large doses of naloxone; doxapram, however, will do so. Severe respiratory depression has occurred when benzodiazepines have been co-administered with buprenorphine.

Buprenorphine is not removed by haemodialysis.

The addition of buprenorphine to local anaesthesia for brachial plexus blockade triples the length of post-operative analgesia compared to local anaesthesia alone.







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Carbamazepine

Uses

Carbamazepine is used in the treatment of:

1. epilepsy, especially temporal lobe and tonic-clonic seizures
2. trigeminal neuralgia and
3. prophylaxis of bipolar disorder.

Chemical

An iminostilbene derivative structurally related to the tricyclic antidepressants.

Presentation

As 100/200/400 mg tablets, 125/250 mg suppositories, and as a white syrup containing 20 mg/ml of carbamazepine.

Main actions

Anticonvulsant and analgesic.

Mode of action

The mode of action of carbamazepine is unknown: it may act via alterations in adenosine disposition within the central nervous system. It does not appear to act in the same manner as tricyclic antidepressants.

Route of administration/doses

The adult oral dose is 100–1600 mg daily in divided doses.

Effects

CVS

Carbamazepine has antiarrhythmic properties and depresses atrio-ventricular conduction.

CNS

The drug is more effective than phenytoin in raising the threshold for minimal electroshock seizures. Carbamazepine also has analeptic properties.

GU

Carbamazepine has an antidiuretic effect that may lead to water intoxication.

Toxicity/side effects

Diplopia, nausea and vomiting, drowsiness, and ataxia are relatively common side effects of the drug. Rashes occur in 3% of patients. Carbamazepine may also cause renal

and liver damage. Mild neutropaenia occurs commonly; fatal aplastic anaemia is extremely rare.

Kinetics

Absorption

The drug is well absorbed when administered orally; the bioavailability by this route is nearly 100%.

Distribution

Carbamazepine is 75% protein-bound in the plasma; the V_D is 1 l/kg.

Metabolism

Occurs via oxidation in the liver to an epoxide which is active. With chronic use, the drug induces its own metabolism.

Excretion

The drug is predominantly excreted in the urine as unconjugated metabolites; the clearance is 20 ml/kg/hour and the elimination half-life is 16–36 hours.

Special points

Sodium valproate and calcium antagonists may increase the plasma concentrations of free carbamazepine if administered concurrently. The efficacy of both pancuronium and vecuronium is reportedly decreased in patients receiving carbamazepine. Regular liver function tests and estimation of white cell counts need to be performed during chronic carbamazepine therapy.

The drug is not removed by haemodialysis.

Carbapenems

Uses

Carbapenems are used in the treatment of infections of:

1. the respiratory tract
2. the urinary tract
3. bone, joint, skin, and soft tissues
4. intra-abdominal sepsis
5. gynaecological sepsis
6. meningitis
7. septicaemia
8. neutropaenic sepsis
9. surgical prophylaxis.

Chemical

Beta lactam derivatives.

Presentation

Imipenem, meropenem, and ertapenem are presented as a dry powder. Imipenem is presented in an ampoule containing 500 mg of imipenem monohydrate and 500 mg of cilastatin sodium, which blocks renal imipenem metabolism. Meropenem is presented in ampoules containing 500 mg and 1 g as meropenem trihydrate. Ertapenem is presented in vials containing 1 g of ertapenem (as ertapenem sodium). Each 1 g dose of ertapenem contains approximately 137 mg of sodium.

Main action

Carbapenems are broad-spectrum antibiotics with activity against:

1. Gram-positive bacteria (not MRSA or *Enterococcus faecalis*)
2. Gram-negative bacteria (not *Stenotrophomonas maltophlia*)
3. Anaerobic bacteria
4. ESBL-producing organisms.

Mode of action

Carbapenems act by binding to penicillin-binding proteins on the bacterial cytoplasmic membrane, thereby blocking peptidoglycan synthesis and thus cell wall formation. Cilastatin sodium, presented with imipenem, is a competitive, reversible inhibitor of dehydropeptidase-1, which mediates the renal metabolism of imipenem. The drug itself has no intrinsic antibacterial activity.

Route of administration/doses

Carbapenems are administered intravenously. The specific dose and frequency of an agent administered is dependent on the clinical indication, age of the patient, and particular agent being used. Doses should be reduced in patients with renal impairment.

Toxicity/side effects

Hypersensitivity reactions, diarrhoea, vomiting, a positive Coombs's test, and pseudomembranous colitis have been reported following the administration of carbapenems. Patients with underlying CNS disorders and/or renal impairment may develop CNS side effects.

Kinetics

Distribution

The V_D for imipenem is 16 l, for meropenem 12.5–20 l, and for ertapenem 8 l. The percentage of drug bound to plasma proteins is 20% for imipenem, 2% for meropenem, and 85–95% for ertapenem.

Metabolism

Imipenem is combined with cilastatin, which prevents renal hydrolysis of the beta lactam ring. However, 20–25% of an administered dose undergoes non-renal systemic metabolism that remains to be fully elucidated. Meropenem is metabolized to an inactive metabolite.

Ertapenem is metabolized to a ring-open derivative following hydrolysis mediated by dehydropeptidase-1.

Excretion

The clearance of imipenem is 225 ml/min (reduced to 194 ml/min when administered with cilastatin) and has a half-life of 62 minutes. The clearance of meropenem is equivalent to creatinine clearance and has a half-life of 60 minutes. Seventy percent of an administered dose of meropenem is excreted unchanged in the urine. The clearance of ertapenem is 207 ml/min and has a half-life of 4 hours. Eighty percent of an administered dose is excreted in the urine (38% unchanged, 37% as the inactive metabolite) and 10% in the faeces.

Special points

Imipenem is cleared by dialysis and the dose should be halved and dose interval doubled. Meropenem and ertapenem are unaffected by hepatic dysfunction. No data is available regarding the use of imipenem in patients with hepatic dysfunction.

Co-administration of imipenem and ganciclovir may lead to focal seizures. Carbapenems may reduce sodium valproate levels, leading to seizure activity.

Carbapenemase-producing organisms such as *Klebsiella pneumoniae* have been isolated.

Antimicrobial agents should always be administered following consideration of local pharmacy and microbiological policies.

Carbon dioxide

Uses

Carbon dioxide is used:

1. to reverse apnoea due to passive hyperventilation
2. to facilitate the inhalational induction of anaesthesia and blind nasal intubation
3. to speed the onset of action of local anaesthetics
4. to increase cerebral blood flow during carotid artery surgery
5. for the insufflation of body cavities during endoscopy
6. for cryotherapy and
7. in the treatment of hiccups.

Chemical

An organic gas.

Presentation

As a liquid in cylinders at a pressure of 50 bar at 15°C; the cylinders are grey and are available in three sizes (C–E, containing 450–1800 l, respectively). Carbon dioxide is a colourless gas with a pungent smell in high concentrations; it is non-flammable and does not support combustion. The specific gravity of the gas is 1.98, the critical temperature 31°C, and the critical pressure 73.8 atmospheres.

Main action

Respiratory and sympathetic stimulation.

Routes of administration/doses

The gas is generally administered by inhalation, but may be insufflated into, for example, the peritoneal cavity. Any concentration that is desired may be employed; concentrations of up to 5% are generally administered by inhalation.

Effects

CVS

In vitro, the gas has negative inotropic and chronotropic effects; *in vivo*, these effects are offset by sympathetic stimulation. The overall effect of the administration of 5% carbon dioxide is to increase the heart rate, systolic and diastolic blood pressures, and cardiac output. Dysrhythmias may occur *in vivo* although *in vitro*, the gas increases the threshold for catecholamine-induced dysrhythmias. The peripheral vascular resistance is decreased *in vivo*; carbon dioxide is a potent coronary arterial vasodilator.

RS

Carbon dioxide (in a concentration of 5%) stimulates respiration by an action on the respiratory centre and peripheral chemoreceptors, leading to an increase in tidal volume and respiratory rate; bronchodilatation is also produced. At high concentrations, respiratory depression occurs. The presence of an increased partial pressure of carbon dioxide in the blood shifts the oxygen dissociation curve to the right (the Bohr effect).

CNS

A $PaCO_2$ of 8–11 kPa will increase the cerebral blood flow by 100% and lead to an increase in intracranial pressure and progressive narcosis. A $PaCO_2$ of 3.5 kPa will reduce cerebral blood flow by 30%.

Metabolic/other

The administration of exogenous carbon dioxide causes a respiratory acidosis which may, in turn, lead to hyperkalaemia. The plasma concentrations of adrenaline, noradrenaline, angiotensin, and 15-hydroxy-corticosteroid are increased by the administration of carbon dioxide.

Toxicity/side effects

When administered in concentrations of 10%, the gas may cause dyspnoea, headache, dizziness, restlessness, paraesthesiae, diaphoresis, and dysrhythmias.

Kinetics

Absorption

The gas is freely permeable through normal alveolar tissue.

Distribution

Carbon dioxide is transported in the blood in solution, in the form of bicarbonate ions, and in combination with plasma proteins and haemoglobin.

Metabolism

The gas is transformed in the blood to the forms described above.

Excretion

Predominantly by exhalation and some as renally excreted bicarbonate.

Special points

A respiratory acidosis may alter drug action by altering both the degree of ionization and protein-binding of drugs; an increased dose of thiopental and a decreased dose of tubocurarine are required in the face of an uncompensated respiratory acidosis.

Cephalosporins

Uses

Cephalosporins are used in the treatment of infections of:

1. the respiratory tract
2. the urinary tract
3. bone, joint, and soft tissues
4. intra-abdominal, gynaecological, and obstetric sepsis
5. meningitis
6. septicaemia and
7. surgical prophylaxis.

Chemical

Derivatives of penicillin containing a beta lactam and a hydrothiazine ring.

Presentation

Cephalosporins are divided into first (cefradine), second (cefuroxime), and third (cefotaxime, ceftazidime, ceftriaxone) generations.

Main action

Cephalosporins are broad-spectrum bactericidal antibiotics that are variably resistant to hydrolysis by beta-lactamase. The drugs are effective against Gram-positive organisms. Gram-negative cover improves with each subsequent generation of cephalosporin (cefradine < cefuroxime < cefotaxime/ceftazidime/ceftriaxone) although this is at the expense of reduced activity against Gram-positive bacteria. Ceftazidime is active against the following organisms: *Pseudomonas*, *Klebsiella*, *Proteus*, *Salmonella*, *Shigella*, *Neisseria* sp., *Haemophilus influenzae*, and *Escherichia coli*.

Mode of action

Cephalosporins act by binding to penicillin-binding proteins on the bacterial cytoplasmic membrane, thereby blocking peptidoglycan synthesis and thus cell wall synthesis.

Route of administration/doses

Cefradine is available in capsule form, as a syrup, or as a powder for dissolving in solution for intravenous use. Cefuroxime is available as a tablet, as granules for use as an oral suspension, or as a powder for dissolving in solution for intravenous administration. Third generation cephalosporins are presented for intravenous use only. The specific dose and frequency of an agent administered is dependent on the clinical indication, age of the patient, and particular agent being used.

Toxicity/side effects

Cephalosporins are generally well tolerated. Rashes, hypersensitivity reactions, fever, diarrhoea, transient haematological disturbances (including a positive Coombs's text), and abnormalities of liver function tests may occur with the use of these drugs. If administered in high doses to patients concurrently receiving other nephrotoxic drugs, further deterioration in renal function may result. *Clostridium difficile* infection may complicate the administration of these agents. The development of a 'Jarisch–Herxheimer' reaction may complicate the use of cephalosporins in the treatment of Lyme disease.

Kinetics

Absorption

Cefradine is well absorbed from the gastrointestinal tract. The bioavailability of cefuroxime is 36–52%.

Distribution

Cephalosporins exhibit variable degrees of protein binding: cefradine 8–17%, cefuroxime and cefotaxime 35–50%, ceftazidime <10%, ceftriaxone 95%. The drugs are widely distributed and third generation agents penetrate inflamed tissues well.

Metabolism

Most cephalosporins are not metabolized apart from cefotaxime which is partially metabolized to the active metabolite, desacetyl-cefotaxime. The half-life for these agents are short (1–2 hours) compared with ceftriaxone which has a half-life of 8 hours.

Excretion

Cephalosporins are predominantly renally excreted unchanged in the urine. 40% of ceftriaxone is excreted in the bile and faeces, 60% in the urine.

Special points

Cephalosporins are removed by haemodialysis.

Cephalosporins are associated with an increased potential for *Clostridium difficile* infection.

Antimicrobial agents should always be administered following consideration of local pharmacy and microbiological policies.

Chlorphenamine

Uses

Chlorphenamine is used in the treatment of:

1. allergic rhinitis
2. urticaria
3. pruritus and
4. anaphylactic and anaphylactoid reactions.

Chemical

An alkylamine.

Presentation

As 4 mg tablets, a syrup containing 0.4 mg/ml, and a clear, colourless solution for injection containing 10 mg/ml of chlorphenamine maleate.

Main action

Antihistaminergic (H1 receptors) and anti-cholinergic.

Mode of action

Chlorphenamine acts by reversible competitive antagonism of histamine H1 receptors.

Route of administration/doses

The adult oral dose is 4 mg 6–8-hourly. The drug may also be administered intravenously (over a period of 1 minute), intramuscularly, or subcutaneously as a stat dose of 10 mg.

Effects

CVS

The drug inhibits histamine-induced vasodilation and increased capillary permeability.

RS

Chlorphenamine decreases bronchial secretions; it does not completely reverse anaphylactic bronchospasm in man, since leukotrienes are involved in the mediation of allergic bronchoconstriction.

CNS

The drug has a sedative effect and local anaesthetic properties.

Metabolic/other

Chlorphenamine has anticholinergic properties.

Toxicity/side effects

The predominant side effect of the drug is drowsiness, but it may also produce gastrointestinal disturbances (including nausea and vomiting) and anticholinergic side effects.

Kinetics

Absorption

The drug is slowly absorbed when administered orally; the bioavailability by this route is 25–50% due to an extensive first-pass metabolism in the gut wall and liver.

Distribution

The drug is 70% protein-bound in the plasma; the V_D is 7.51–7.65 l/kg.

Metabolism

Occurs via demethylation and oxidative deamination in the liver.

Excretion

The mono- and di-desmethyl derivatives are excreted predominantly in the urine; 1–27% (dependent upon the urinary pH) of an administered dose is excreted unchanged in the urine. The clearance is 4.4–7.92 ml/min/kg and the elimination half-life is 2–43 hours.

Special points

The sedative effect of the drug is additive with that produced by anaesthetic agents.

The drug is not removed by dialysis.

Chlorpromazine

Uses

Chlorpromazine is used in the treatment of:

1. schizophrenia and related psychoses
2. nausea and vomiting associated with terminal illness and
3. intractable hiccup.

Chemical

A phenothiazine (with an aliphatic side chain).

Presentation

As 10/25/50/100 mg tablets, a syrup containing 5 mg/ml, 100 mg suppositories, and as a straw-coloured solution for injection containing 25 mg/ml of chlorpromazine hydrochloride.

Main action

Antipsychotic, antiemetic, and sedative.

Mode of action

The antiemetic and neuroleptic effects of the drug appear to be mediated by central dopaminergic (D2) blockade, leading to an increased threshold for vomiting at the chemoreceptor trigger zone. The other pharmacological effects are mediated by antagonism of serotonergic, histaminergic, muscarinic cholinergic, and alpha-adrenergic receptors.

Route of administration/doses

The adult oral dose is 10–50 mg 6–8-hourly; the corresponding dose by the intramuscular route is 25–50 mg 6–8-hourly.

Effects

CVS

Chlorpromazine is negatively inotropic; in combination with the decrease in systemic vascular resistance mediated by alpha-adrenergic blockade that it produces, postural hypotension with a reflex tachycardia are the main effects observed. The drug increases coronary blood flow and has a mild quinidine-like action on the heart. Chlorpromazine may produce ECG changes, including prolongation of the PR and QT intervals, T wave flattening, and ST segment depression.

RS

The drug is a respiratory depressant; it also diminishes bronchial secretions.

CNS

The main central effect of the drug is neurolepsis, but sedation and anxiolysis are also produced. Chlorpromazine enhances the effect of co-administered analgesics and lowers the seizure threshold; it also has local anaesthetic properties. The drug causes skeletal muscle relaxation via a central effect. Miosis occurs due to alpha-adrenergic blockade. It increases sleep time, but decreases the time spent in the REM phase. The characteristic EEG changes associated with the use of chlorpromazine are slowing with an increase in theta- and delta-wave activity and a decrease in alpha- and beta-wave activity, activity.

AS

Chlorpromazine increases appetite and may cause weight gain; it tends to decrease salivation, gastric secretion, and gastrointestinal motility.

GU

The drug increases renal blood flow and has a weak diuretic action. Ejaculation and micturition may be inhibited secondary to the anticholinergic effect of the drug.

Metabolic/other

Chlorpromazine impairs temperature regulation by both central and peripheral mechanisms; anaesthetized subjects receiving the drug show a tendency to become poikilothermic. The phenothiazines increase prolactin secretion and tend to decrease adrenocorticotrophic and antidiuretic hormone release. Insulin release and thus glucose tolerance may also be impaired by the drug.

Toxicity/side effects

Chlorpromazine is generally a well-tolerated and safe drug, despite its panoply of effects. The drug may produce a variety of extrapyramidal syndromes, including the rare neuroleptic malignant syndrome (a complex of symptoms that include catatonia, cardiovascular lability, hyperthermia, and myoglobinaemia) which has a mortality in excess of 10%. A variety of anticholinergic effects, jaundice, blood dyscrasias, and allergic phenomena may also complicate the use of the drug.

Kinetics

Absorption

Chlorpromazine is well absorbed when administered orally, but has a bioavailability by this route of 30% due to an extensive first-pass metabolism in the liver and gut wall.

Distribution

The drug is 95–98% protein-bound in the plasma; the V_D is 12–30 l/kg.

Metabolism

Chlorpromazine is extensively metabolized in the liver by oxidation, dealkylation, demethylation, and hydroxylation with subsequent conjugation to glucuronide; at least 168 metabolites have been described, many of which are active.

Excretion

Occurs in equal quantities in the urine and faeces; less than 1% is excreted unchanged. The clearance is 5.7–11.5 ml/min/kg and the elimination half-life is 30 hours.

Special points

The depressant effects of chlorpromazine are additive with those produced by general anaesthetic agents.

The drug is not removed by haemodialysis.

Cisatracurium

Uses

Cisatracurium is used to facilitate intubation and controlled ventilation.

Chemical

A benzyl isoquinolinium ester which is one of ten stereoisomers of atracurium due to the presence of four chiral centres.

Presentation

As a clear colourless or pale-yellow solution for injection available in 5, 10, 20 and 30 ml vials containing 6.7mg/ml of cisatracurium besilate (equivalent to cisatracurium 5mg/ml) needing to be stored at 2–8ºC. A 2 mg/ml preparation is also available in a 10 ml ampoule. It contains no antimicrobial preservative. It has a pH of between 3.25 and 3.65.

Main Action

Competitive non-depolarising neuromuscular blockade.

Mode of Action

Cisatracurium acts by competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction.

Route of Administration/Dose

The drug is administered intravenously. The ED_{95} of cisatracurium is estimated to be 0.05 mg/kg during opioid anaesthesia. An initial dose of 0.15mg/kg is recommended providing good to excellent intubating conditions in 120 seconds. The time to 90% T1 suppression following this dose is 2.6 minutes, the time to maximal T1 suppression is 3.5 minutes, and the time to 25% spontaneous T1 recovery is 55 minutes. Maintenance of neuromuscular blockade may be achieved with bolus doses of 0.03mg/kg (0.02mg/kg in paediatric patients) which will provide approximately 20 minutes of additional neuromuscular blockade (approximately 9 minutes in paediatric patients). Once recovery from neuromuscular blockade has started, the rate of recovery is independent of the dose of cisatracurium administered. Cisatracurium may be administered by intravenous infusion at an initial rate of 3mcg/kg/min (0.18 mg/kg/hr) although there is wide inter-patient variability in dosage requirements, particularly in patients ventilated on intensive care. This infusion rate should result in T1 suppression of between 89-99%. After an initial period of stabilisation of neuromuscular block, a rate of 1–2 mcg/kg/min (0.06–0.12 mg/kg/min) is recommended to maintain adequate blockade (0.03–0.06 mg/kg/min in patients ventilated on intensive care). Following long-term continuous infusion of cisatracurium (<6days), the median time to full spontaneous recovery was approximately 50 minutes. When used in conjunction with isoflurane maintenance, the infusion rate may be reduced by up to 40%. The use of cisatracurium in patients undergoing induced hypothermia (25–28ºC) has not been studied.

Effects

CVS

Cisatracurium has fewer cardiovascular effects than atra-curium. There is no change in mean arterial pressure or heart rate following rapid bolus doses of 0.1–0.4 mg/kg in healthy adults and patients with severe cardiovascular disease. Bra-dycardia (0.4%), hypotension (0.2%) and cutaneous flushing (0.2%) have all been reported.

RS

Bronchospasm following administration of cisatracurium has been occasionally reported (approximately 0.2%).

CNS

The drug has no effect on intracranial or intraocular pressure.

AS

Lower oesophageal sphincter pressure is unaffected by administration of cisatracurium.

Toxicity/Side Effects

There is no dose-dependant increase in histamine release following administration of cisatracurium at doses of 0.1–0.4 mg/kg. There have been rare reports of fatal anaphylactoid reactions with the administration of atracurium. Administration of cisatracurium by intravenous infusion to critically ill patients on intensive care has been associated with development of a critical illness neuropathy/myopathy.

Kinetics

Distribution

The binding of cisatracurium has not been determined due to its rapid degradation at physiological pH. The V_D at steady state is 0.12–0.16 l/kg.

Metabolism

Occurs by two pathways; the major pathway is via Hofmann degradation (cleavage of the link between the quaternary nitrogen ion and the central chain) to laudanosine and a quaternary monacrylate. Laudanosine is cleared primarily by the liver. The minor degradative pathway is via hydrolysis by non-specific esterases in the blood to a quaternary alcohol and a quaternary acid. The metabolites have insignificant neuromuscular-blocking activity.

Excretion

The clearance is 4.7–5.7 ml/kg/min and the elimination half-life is 22–29 minutes; these parameters are altered little by renal or hepatic impairment and no alteration in dose is necessary in these patients. A study in healthy adults demonstrated that 95% of the dose of cisatracurium is excreted in the urine (mostly as conjugated metabolites), and 4% in the faeces. Between 10 and 15% of an administered dose is excreted unchanged in the urine.

Special Points

The duration of action of cisatracurium, in common with other non-depolarising relaxants, is prolonged by hypokalaemia, hypocalcaemia, hypermagnesaemia, hypoproteinaemia, dehydration, acidosis, and hypercapnia. The following drugs, when co-administered with atracurium, increase the effect of the latter: volatile anaesthetic agents, ketamine, other non-depolarising neuromuscular blocking agents, diuretics (frusemide, mannitol, acetazolamide), calcium channel blockers, propanolol, lignocaine, aminoglycoside antibiotics, magnesium and lithium salts. A decreased effect may be seen in patients receiving chronic anticonvulsant therapy.

The C_{max} values of laudanosine are lower in patients receiving intravenous infusions of cisatracurium compared with those receiving a continuous atracurium infusion. No dose alteration is required in patients with renal or hepatic impairment, al-though the $t_{½β}$ values of metabolites are prolonged in patients with renal impairment.

Cisatracurium, due to its acidic pH, should not be mixed with alkaline solutions (e.g. barbiturates). It is not compatible with propofol or ketorolac. The drug is compatible with the follow-ing agents: alfentanil, fentanyl, sufentanil, and midazolam.

Porcine studies indicate that cisatracurium does not trigger malignant hyperthermia, although the drug has not been stud-ied in susceptible humans.

Clomethiazole

Uses

Clomethiazole is used:

1. in the management of alcohol withdrawal states
2. as an anticonvulsant (emergency use only)
3. as a hypnotic for the elderly
4. in the treatment of eclampsia and pre-eclampsia and
5. for sedation in patients undergoing surgery under regional blockade or intensive care.

Chemical

A thiamine derivative.

Presentation

As a clear, aqueous solution containing 8 mg/ml of clomethiazole edisylate, and in 192 mg capsule and 50 mg/ml syrup form.

Main action

Anticonvulsant, sedative, and anxiolytic.

Mode of action

The anticonvulsant and sedative actions are due to enhancement of central GABA-ergic transmission and possibly inhibition of central dopaminergic transmission.

Route of administration/doses

For the control of convulsions in adults, 40–100 ml of the 0.8% solution are infused intravenously over 5–10 minutes; subsequently, the infusion rate is tailored to the response. For sedation, 25 ml/min are administered intravenously for 1–2 minutes, followed by a maintenance infusion of 1–4 ml/min. As a hypnotic, 1–2 capsules or 5–10 ml of the syrup are administered orally.

Effects

CVS

Tachycardia and hypotension are the only clinically significant effects of the drug. It is also powerfully amnesic.

RS

No effects are seen with the use of clomethiazole, but at high doses, airway obstruction may occur.

CNS

Clomethiazole has anticonvulsant, sedative, and hypnotic properties.

Toxicity/side effects

Nasal and conjunctival irritation, headache, and increased bronchial secretions may occur. Prolonged intravenous infusion of clomethiazole may lead to volume overload and electrolyte abnormalities due to the water load involved. Renal failure has been reported after prolonged use associated with hypotension. Physical dependence and withdrawal states have been reported following chronic use of the drug.

Kinetics

Absorption

Clomethiazole is well absorbed when administered orally; the bioavailability by this route is 25–34% due to a high hepatic clearance.

Distribution

The drug is 65–70% protein-bound in the plasma, predominantly to albumin; the V_D is 3–5 l/kg.

Metabolism

Occurs predominantly by oxidation in the liver; there is an extensive first-pass effect. 10–20% is metabolized in the lung; there may also be some renal extraction of the drug.

Excretion

0.1% is excreted unchanged in the urine. The clearance is 2.1 l/min and the elimination half-life is 1–6 hours.

Special points

Clomethiazole is absorbed by plastic giving-sets.

It is removed by haemodialysis, but this may not significantly affect the degree of sedation.

Clonidine

Uses

Clonidine is used in the treatment of:



1. all grades of essential and secondary hypertension
2. hypertensive crises and in the management of
3. migraine
4. menopausal flushing and may be of use in
5. chronic pain
6. during opiate and alcohol withdrawal and
7. for intravenous regional analgesia for chronic regional pain syndromes.

Chemical

An aniline derivative.

Presentation

As 0.1/0.25/0.3 mg tablets and as a clear, colourless solution for injection containing 0.15 mg/ml of clonidine hydrochloride.

Main action

Antihypertensive, analgesic, sedative, and anxiolytic.

Mode of action

Clonidine acts acutely by stimulating alpha-2 (pre-synaptic) adrenoceptors, thereby decreasing noradrenaline release from sympathetic nerve terminals and consequently decreasing sympathetic tone; it also increases vagal tone. The drug acts chronically by reducing the responsiveness of peripheral vessels to vasoactive substances and to sympathetic stimulation. The analgesic effects are also mediated by activation of alpha-2 adrenoceptors in the dorsal horn of the spinal cord.

Route of administration/doses

The adult oral dose is 0.05–0.6 mg 8-hourly; the corresponding intravenous dose is 0.15–0.3 mg. When administered by the epidural route, a dose of 0.15 mg has been used. The drug acts within 10 minutes and lasts for 3–7 hours when administered intravenously.

Effects

CVS

When administered intravenously, clonidine causes a transient increase in the blood pressure (due to the stimulation of vascular alpha-1 receptors) followed by a sustained decrease. The heart rate and venous return may decrease slightly; the drug has no effect on cardiac contractility and cardiac output is well maintained. The coronary vascular resistance is decreased by clonidine; the systemic vascular resistance is decreased with long-term treatment.

CNS

Clonidine decreases cerebral blood flow and intraocular pressure. It exerts a depressant effect on both spontaneous sympathetic outflow and afferent A delta- and C-fibre-mediated somatosympathetic reflexes.

AS

Clonidine decreases gastric and small bowel motility and is an antisialogogue.

GU

Clonidine reduces renovascular resistance; however, little alteration in the glomerular filtration rate occurs.

Metabolic/other

The drug causes a decrease in plasma catecholamine concentrations and plasma renin activity. Blood sugar concentration may increase secondary to alpha-adrenergic stimulation.

Toxicity/side effects

Drowsiness and a dry mouth may occur in up to 50% of patients who receive the drug. Central nervous system disturbances, fluid retention, impotence, and constipation have also been reported. Rapid withdrawal of the drug may lead to life-threatening rebound hypertension and tachycardia.

Kinetics

Absorption

The drug is rapidly and well absorbed when administered orally; the oral bioavailability is 100%.

Distribution

Clonidine is very lipid-soluble and penetrates the central nervous system. The drug is 20% protein-bound in the plasma; the V_D is 1.7–2.5 l/kg.

Metabolism

Less than half of an administered dose is metabolized in the liver to inactive metabolites.

Excretion

65% of the dose of clonidine is excreted unchanged in the urine; some 20% is excreted in the faeces. The clearance is 1.9–4.3 ml/min/kg and the elimination half-life is 6–23 hours. The latter is markedly increased in the presence of renal impairment; the dose of clonidine should be reduced if the glomerular filtration rate is 10 ml/min.

Special points

Clonidine decreases the MAC of co-administered volatile agents. It decreases the incidence of post-anaesthetic shivering and post-operative nausea and vomiting.

Clonidine decreases the propofol dose needed for LMA insertion.

It obtunds tourniquet-induced hypertension.

Clonidine decreases post-operative agitation in children undergoing sevoflurane anaesthesia.

It prolongs the duration of local anaesthesia when co-administered for neural and retrobulbar blockade.

The drug is not removed by haemodialysis.

Cocaine

Uses

Cocaine is used as a topical vasoconstrictor.

Chemical

An ester of benzoic acid (a naturally occurring alkaloid derived from the leaves of *Erythroxylon coca*).

Presentation

As 1–4% solutions and as a non-proprietary paste of varying concentration.

Main action

Local anaesthesia, vasoconstriction, and euphoria.

Mode of action

Local anaesthetics diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels; here they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the cell membrane. Cocaine also produces blockade of the uptake-1 pathway of noradrenaline and dopamine, leading to vasoconstriction and central nervous system excitation.

Route of administration/doses

Cocaine is administered topically; the toxic dose is 3 mg/kg. The drug has duration of action of 20–30 minutes.

Effects

CVS

The usual effect of cocaine is to produce hypertension and tachycardia due to a combination of central sympathetic stimulation and the blockade of noradrenaline re-uptake at peripheral adrenergic nerve terminals, leading to intense peripheral vasoconstriction. Large doses produce myocardial depression and may precipitate ventricular fibrillation.

RS

Therapeutic concentrations of the drug cause stimulation of the respiratory centre and an increase in ventilation.

CNS

The principal effect of cocaine is reversible neural blockade; this leads to a characteristically biphasic effect in the central nervous system. Initially, excitation (euphoria, lightheadedness, dizziness, visual and auditory disturbances, and fitting) occurs due to the blockade of inhibitory pathways in the cortex; with increasing doses, depression of both facilitatory and inhibitory pathways occurs, leading to central nervous system depression (drowsiness, disorientation, and coma). Cocaine may also cause hyperreflexia, mydriasis, and an increase in intraocular pressure.

AS

The drug produces hyperdynamic bowel sounds and marked nausea and vomiting (a central effect).

Metabolic/other

Cocaine causes a marked increase in body temperature due to increased motor activity combined with cutaneous vasoconstriction and a direct effect of the drug on the hypothalamus.

Toxicity/side effects

Allergic phenomena occur occasionally with the use of cocaine. The side effects are predominantly correlated with excessive plasma concentrations of the drug. These include confusion, hallucinations, seizures, cerebral haemorrhage and infarction, and medullary depression leading to respiratory arrest. Chest pain is common; myocardial infarction, pulmonary oedema, gut infarction, rhabdomyolysis, and disseminated intravascular coagulation may also occur. Cocaine is a drug of dependence; maternal use may result in neonatal dependence. Nasal septum necrosis is reported.

Kinetics

Absorption

The drug is well absorbed from mucosae, including that of the gut. The bioavailability when administered intranasally is 0.5%.

Distribution

Cocaine is 98% protein-bound in the plasma; the V_D is 0.9–3.3 l/kg.

Metabolism

In common with the other ester-type local anaesthetic agents, cocaine is predominantly degraded by plasma esterases, predominantly to benzoylecgonine.

Excretion

The metabolites are excreted in the urine, 10% unchanged. The clearance is 26–44 ml/min/kg and the elimination half-life is 25–60 minutes.

Codeine

Uses

Codeine is used for the treatment of:

1. pain of mild to moderate severity
2. diarrhoea and excessive ileostomy output and
3. as an antitussive agent and
4. traditionally to provide analgesia for head-injured patients.

Chemical

A naturally occurring phenanthrene alkaloid which is a methylated morphine derivative.

Presentation

As 15/30/60 mg tablets, a syrup containing 5 mg/ml, and as a clear, colourless solution for injection containing 60 mg/ml of codeine phosphate. A number of fixed dose preparations containing paracetamol, ibuprofen, or aspirin in combination with codeine phosphate are also available.

Main action

Analgesic, antitussive, and a decrease in gastrointestinal motility.

Mode of action

Codeine has a very low affinity for opioid receptors; 10% of the drug is metabolized to morphine and the analgesic and constipating effects are due to the morphine metabolite. The antitussive effects of codeine appear to be mediated by specific, high-affinity codeine receptors.

Route of administration/doses

The adult oral and intramuscular dose is 30–60 mg 4–6-hourly. Rectal administration in a dose of 1 mg/kg can be used in paediatrics. It should not be given intravenously due to hypotension probably due to histamine release.

Effects

RS

The principal effect of the drug is an antitussive effect; it also produces some respiratory depression with a decreased ventilatory response to hypoxia and hypercapnia.

CNS

Codeine is ten times less potent an analgesic compared to morphine and produces few of the central effects associated with opioids.

AS

The drug markedly inhibits gastrointestinal motility, leading to constipation.

Toxicity/side effects

Nausea and vomiting, dizziness, and excitatory phenomena may complicate the use of the drug; cardiovascular collapse may occur when codeine is taken in overdose or administered intravenously. Bowel perforation secondary to decreased gastrointestinal transit has been reported. Codeine has a low propensity to cause dependence.

Kinetics

Absorption

Codeine phosphate is well absorbed when administered orally and rectally; the bioavailability by these routes is 60–70% as little first-pass metabolism of the drug occurs. Absorption is faster after intramuscular absorption (0.5 hours). Peak concentration occurs at 1 hour.

Distribution

Codeine is 7% protein-bound in the plasma; the V_D is 5.4 l/kg.

Metabolism

Codeine is extensively metabolized in the liver by three methods: principally (10–20%) by glucuronidation to codeine-6-glucuronide, by N-demethylation (10–20%) to norcodeine, and by O-demethylation to morphine (5–15%).

Other minor metabolites, normorphine, norcodeine-6-glucuronide, have been found.

Genetic variability occurs with the cytochrome P450 enzyme, CYP2D6, which causes conversion to morphine, so 'fast' metabolizers produce more morphine.

Excretion

Occurs predominantly in the urine as free and conjugated codeine, norcodeine, and morphine; 17% of the dose is excreted unchanged. The clearance is 98 l/hour after oral administration and the elimination half-life is 2.8 hours. The dose should be reduced in the presence of renal failure.

Special points

There are no published data to support the use of codeine in the management of head-injured patients. The drug has traditionally been used in these circumstances due to its low potency and consequent relative lack of respiratory and neurological depressant effects.

Co-trimoxazole

Uses

Co-trimoxazole should be used in the treatment of:

1. *Pneumocystis carinii* infections
2. toxoplasmosis and
3. nocardiasis.

Chemical

(Trimethoprim-1-sulfamethoxazole) Trimethoprim is a diaminopyrimidine and sulfamethoxazole is a sulphonamide.

Presentation

All preparations contain trimethoprim and sulfamethoxazole in the ratio of 1:5. The tablets contain 20/80/160 mg of trimethoprim in a fixed dose combination with 100/400/800 mg of sulfamethoxazole, respectively. A suspension for oral administration is also available. A pale yellow preparation of co-trimoxazole is available for intravenous use and contains 16 mg of trimethoprim and 80 mg of sulfamethoxazole per ml. The intramuscular preparation contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole in 3

ml.

Main action

Co-trimoxazole is bactericidal against a broad spectrum of Gram-positive and Gram-negative aerobic bacteria, including the Gram-positive *Staphylococcus* and *Streptococcus* spp., the Gram-negative *Proteus*, *Salmonella*, *Shigella* and *Klebsiella* spp., and *Escherichia coli*. It is also effective against some protozoa, *Chlamydia* sp., and some anaerobic species. Bacterial resistance to the drug is widespread.

Mode of action

Co-trimoxazole inhibits the synthesis of tetrahydrofolic acid which is needed for the synthesis of nucleic acids and amino acids. The two components of the drug act at separate stages in the biosynthetic pathway of tetrahydrofolic acid; sulfamethoxazole inhibits the synthesis of dihydrofolic acid and trimethoprim is a competitive inhibitor of dihydrofolate reductase. Mammalian dihydrofolate reductase is minimally affected by co-trimoxazole; in any case, mammalian cells utilize preformed folate derived from the diet.

Route of administration/doses

The adult oral dose is 2–3 of the 80/400 mg tablets 12-hourly. The corresponding dose by the intravenous or intramuscular route is 160/800 to 240/1200 mg 12-hourly. The intravenous preparation should be diluted in a crystalloid prior to use and infused over a period of 90 minutes.

Effects

Metabolic/other

Serum creatinine concentrations may increase with the use of the drug due to competition for tubular secretory mechanisms and to an effect on the assay of creatinine. The plasma concentration of thyroid hormone may also decrease.

Toxicity/side effects

The use of co-trimoxazole may be complicated by allergic phenomena, and gastrointestinal and haematological disturbances, especially neutropaenia. Patients known to be deficient in vitamin B_{12} or folate are at increased risk for the latter complication.

Kinetics

Absorption

Both components of the drug are well absorbed; the bioavailability of both sulfamethoxazole and trimethoprim is 100%.

Distribution

The plasma ratio of trimethoprim:sulfamethoxazole is 1:20, which appears to be optimal for synergistic activity. Trimethoprim is 45% protein-bound in the plasma; its V_D is 1.6–2.0 l/kg. Sulfamethoxazole is 66% protein-bound in the plasma; its V_D is 0.19–0.23 l/kg.

Metabolism

5–15% of the dose of trimethoprim is metabolized to inactive products; sulfamethoxazole is extensively metabolized, the major metabolite being an acetyl derivative.

Excretion

Both components are excreted predominantly in the urine; 80% of the dose of trimethoprim is excreted unchanged whereas sulfamethoxazole is excreted predominantly as inactive metabolites. The clearance of trimethoprim is 1.6–2.8 ml/min/kg and the elimination half- life is 11 hours. The clearance of sulfamethoxazole is 0.28–0.36 ml/min/kg and the elimination half-life is 9 hours. The dose of co-trimoxazole should be reduced if the creatinine clearance is 30 ml/min; hepatic impairment has no effect on the kinetics of the drug.

Special points

Co-trimoxazole potentiates the anticoagulant effect of co-administered warfarin and the hypoglycaemic effect of co-administered sulphonylureas. The drug has a theoretically synergistic action with nitrous oxide on folic acid metabolism. Both components of the drug are haemodialysable.

Cyclizine

Uses

Cyclizine is used in the treatment of nausea and vomiting due to:

1. opioid or general anaesthetic agents
2. motion sickness
3. radiation sickness and
4. Menière's disease.

Chemical

A piperazine derivative.

Presentation

As tablets containing 50 mg of cyclizine hydrochloride and as a clear, colourless solution for injection containing 50 mg/ml of cyclizine lactate which should be protected from light. Fixed dose combinations with morphine, caffeine, ergotamine, and dipipanone are available. It has a pH of 3.2.

Main action

Antiemetic.

Mode of action

Cyclizine is a competitive antagonist of histamine at H1 receptors and has anticholinergic activity at the muscarinic, M1, M2, and M3, receptors. The antiemetic effect is mediated via blockade of central histamine and muscarinic receptors within the vomiting area of the chemoreceptor trigger zone. Cyclizine produces its antiemetic effect within 2 hours and lasts approximately 4 hours.

Routes of administration/doses

Cyclizine may be given orally or by intramuscular or intravenous injection. Given the low pH of the parenteral preparation, injection by either route may be painful. The maximum daily dose is 150 mg. The paediatric dose is 1 mg/kg.

Effects

CVS

The drug has mild anticholinergic action and can produce tachycardia and hypotension due to alpha-blockade.

RS

Cyclizine, although it has antihistaminergic properties, does not completely reverse anaphylactic bronchospasm as leukotrienes are involved in the mediation of allergic bronchoconstriction.

CNS

The principle effect of the drug is an antiemetic effect with a slight degree of sedation. Cyclizine reduces the sensitivity of the labyrinthine apparatus and depresses vestibular stimulation.

AS

Cyclizine increases the tone of the lower oesophageal sphincter.

Toxicity/side effects

The predominant side effects are anticholinergic, including drowsiness, dryness of the mouth, and blurred vision. Restlessness, nervousness, insomnia, and auditory and visual hallucinations have been reported. Confusion in the elderly is common.

Kinetics

Data are incomplete.

Absorption

The drug is well absorbed when administered orally; the bioavailability by this route is 80%. Following oral administration of 50 mg of cyclizine, peak plasma concentrations of 70 ng/ml occur at approximately 2 hours.

Metabolism

Cyclizine is metabolized in the liver by N-demethylation to norcyclizine. Norcyclizine has little antihistamine activity.

Elimination

The elimination half-life is 10–20 hours. Limited data suggest that only 1% of the total administered dose is excreted, unchanged in the urine.

Special points

Cyclizine appears to be as effective as perphenazine in counteracting the nausea and vomiting associated with the use of opioids. The sedative effect of the drug is additive with that produced by anaesthetic agents.

The drug should be used with caution in patients with severe heart failure as a fall in cardiac output may occur following the administration of cyclizine, secondary to increases in heart rate, mean arterial pressure, and pulmonary capillary wedge pressure.

The drug should be avoided in patients with porphyria.



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Dabigatran

Uses

Dabigatran is used for the primary prevention of:

1. venous thromboembolic events post-elective total hip replacement and
2. venous thromboembolic events post-elective total knee replacement surgery.

Chemical

A benzamidine-based thrombin inhibitor.



Presentation

As 75/110 mg capsules containing dabigatran etexilate.

Main actions

Competitive, reversible, direct thrombin inhibitor.

Mode of action

Dabigatran etexilate is a pro-drug. Following oral administration, it undergoes plasma and hepatic esterase-catalyzed hydrolysis to dabigatran which acts as a direct thrombin inhibitor. Inhibition of thrombin prevents cleavage of fibrinogen to fibrin. The drug also inhibits:

1. free thrombin
2. fibrin-bound thrombin and
3. thrombin-induced platelet aggregation.

Route of administration/doses

Dabigatran is available in 75 and 110 mg capsules as dabigatran mesilate. The recommended dose for prevention of venous thromboembolism following elective knee replacement surgery is 110 mg, taken 1 to 4 hours after surgery followed by 220 mg once daily for 10 days. The recommended dose following elective hip replacement surgery is the same, but treatment is continued for 28 to 35 days. The dose should be reduced in the elderly and in patients with moderate renal impairment to 75 mg, taken 1 to 4 hours after surgery followed by 150 mg once daily.

Effects

Metabolic/other

In addition to its anticoagulant effects, dabigatran inhibits platelet aggregation.

Toxicity/side effects

Excessive bleeding is the most commonly reported side effect (14% of patients). The colorant 'sunset yellow' is present within capsules of dabigatran which has been associated with allergic reactions. The use of neuroaxial blocks in patients receiving the drug must be carefully considered, and the timing of block/catheter insertion/removal and commencement/withholding/discontinuation of dabigatran must be appropriately timed to minimize the risk of spinal/epidural haematoma formation.

Kinetics

Absorption

Dabigatran is rapidly converted from its etexilate form to the active drug via esterase hydrolysis. The bioavailability of the drug is 6.5%. Following oral administration, C_{max} is reached within 0.5 to 2 hours.

Distribution

The drug is 35% protein-bound in plasma; the V_D is 60–70 l.

Metabolism

Dabigatran is metabolized by conjugation to active acylglucuronides. Four isomers may exist: 1-O, 2-O, 3-O, and 4-O-acylglucuronide, accounting for less than 10% of total drug in the plasma.

Excretion

The drug is excreted predominantly unchanged in the urine at a rate proportional to the glomerular filtration rate. Plasma levels of the drug demonstrate a bi-exponential decline with a terminal elimination half-life of 12–14 hours. 6% of an administered dose is excreted in faeces. Renal impairment increases the time of drug exposure. Consequently, the dose should be reduced in moderate renal impairment and the drug should be avoided in patients with severe renal impairment. Limited data from patients with hepatic impairment did not demonstrate increased time of drug exposure following the administration of dabigatran.

Special points

The use of unfractionated heparin, low molecular weight heparins, fondaparinux, desirudin, thrombolytic agents, glycoprotein IIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone, and vitamin K antagonists are not recommended in patients concurrently receiving dabigatran.

The time of drug exposure is increased when dabigatran is administered to patients concurrently receiving amiodarone and the daily dose should be reduced to 150 mg of dabigatran daily. The mechanism of this interaction has not been fully elucidated. However, amiodarone is an inhibitor of the efflux transporter P-glycoprotein of which dabigatran is a substrate. Strong inhibitors of the efflux transporter, P-glycoprotein, include verapamil and clarithromycin. The use of the drug should be used with caution in patients receiving these drugs. Dabigatran should not be administered to patients also receiving the P-glycoprotein inhibitor, quinidine.

The time of drug exposure may be reduced when dabigatran is administered to patients concurrently receiving P-glycoprotein inducers such as rifampicin and *Hypericum perforatum* (St John's Wort).

There is no antidote currently available for dabigatran.

The drug may be removed by haemodialysis.

Dantrolene

Uses

Dantrolene is used in the treatment of:

1. malignant hyperthermia and the neuroleptic malignant syndrome
2. heat stroke and
3. muscle spasticity and may be of use
4. as an adjunct in the treatment of tetanus.

Chemical

A phenyl hydantoin derivative.

Presentation

As 25 or 100 mg capsules of dantrolene sodium as a lyophilized orange powder which contains 20 mg of dantrolene sodium and 3 g of mannitol (to improve the solubility), together with sodium hydroxide in each vial; this is reconstituted prior to use with 60 ml of water. A solution of pH 9.5 is produced.

Main action

Muscular relaxation.

Mode of action

Dantrolene acts within skeletal muscle fibres to inhibit calcium ion release through the inhibition of ryanodine receptors in the sarcoplasmic reticulum to cause a reduction in muscular contraction to a given electrical stimulus. Part of its action may be due to a marked GABA-ergic effect.

Route of administration/doses

For the treatment of acute hyperthermia, 1–10 mg/kg administered intravenously (either via a central vein or into a fast-running infusion) as required—an average of 2.5 mg/kg is required. For the prophylaxis of malignant hyperthermia, 4–8 mg/kg/day are given for 1–2 days prior to surgery in 3 to 4 divided doses; the role of this regime is controversial. The oral adult dose used for the prevention of spasticity is 25–100 mg 6-hourly. Therapeutic effects are observed within 15 minutes; the mean duration of action is 4–6 hours.

Effects

CVS

No consistent effects have been reported from animal studies. Dantrolene may have antiarrhythmic effects in man. Dantrolene improves beta-adrenergic responsiveness in the

failing human myocardium.

RS

Negligible effects are produced by the drug in man.

CNS

Dantrolene has marked central GABA-ergic effects; sedation may occur.

GU

Dantrolene increases the effectiveness of voiding in many patients with neuromuscular disorders.

Metabolic/other

Dantrolene diminishes the force of electrically induced muscle twitches whilst having no effect on action potentials in skeletal muscle.

Toxicity/side effects

The drug is highly irritant if extravasated. With chronic use, muscular weakness, drowsiness, and gastrointestinal disturbances may occur. Hepatic dysfunction occurs in up to 2% of patients which is reversible.

Kinetics

Absorption

20–70% of an oral dose is absorbed.

Distribution

Dantrolene is 80–90% protein-bound to albumin. The V_D is 0.6 l/kg.

Metabolism

Predominantly in the liver by hydroxylation (to an active metabolite) and by reduction and acetylation.

Excretion

15–25% is excreted in the urine, predominantly as the hydroxy metabolite. The clearance is 2.3 ml/kg/min and elimination half-life is 3–12 hours.

Special points

There are no controlled trials of the effectiveness of dantrolene in the treatment of malignant hyperthermia or the malignant neuroleptic syndrome in man; however, more than 80% of patients with prodromal signs of the syndromes improve after receiving dantrolene. It has also been used successfully in the management of ‘Ecstasy’ toxicity.

Verapamil and dantrolene administered concurrently in animals may cause hyperkalaemia, leading to ventricular fibrillation; these drugs are not recommended for use together in man.

Desflurane

Uses

Desflurane is used for the induction and maintenance of general anaesthesia.

Chemical

A fluorinated methylethylether.

Presentation

As a clear, colourless liquid that should be protected from light. The commercial preparation contains no additives and is flammable at a concentration of 17%. The molecular weight of desflurane is 168, the boiling point is 22.8°C, and the saturated vapour pressure is 88.5 kPa at 20°C. The MAC of desflurane is age-dependent and ranges from 5.1790.65% to 10.65% (1.6790.4% to 7.75% in the presence of 60% nitrous oxide), the blood/gas partition coefficient is 0.45, and the fat/blood partition coefficient is 29. Desflurane is stable in the presence of moist soda lime.

Main action

General anaesthesia (reversible loss of both awareness and recall of noxious stimuli).

Mode of action

The mechanism of general anaesthesia remains to be fully elucidated. General anaesthetics appear to disrupt synaptic transmission (especially in the area of the ventrobasal thalamus). This mechanism may include potentiation of the GABA and glycine receptors and the antagonism at NMDA receptors. Their mode of action at the molecular level appears to involve expansion of hydrophobic regions in the neuronal membrane, either within the lipid phase or within hydrophobic sites in cell membranes.

Routes of administration/doses

Desflurane is administered by inhalation. Because of the high saturated vapour pressure, desflurane must be administered by a specific pressurized and heated vaporizer. The concentration used for induction of anaesthesia is quoted as 4–11% although induction is usually achieved using a different agent. Maintenance of anaesthesia is usually achieved using between 2–6%.

Effects

CVS

Desflurane causes a decrease in myocardial contractility, but sympathetic tone is relatively well preserved. The cardiac index and left ventricular ejection fraction are well preserved in man. Desflurane causes a dose-dependent decrease in systemic vascular resistance and mean arterial pressure; the heart rate may increase via an indirect autonomic effect, particularly at inspired concentrations of 9% or greater. The drug does not appear to cause the 'coronary steal' phenomenon in man. Desflurane does not sensitize the myocardium to the effects of catecholamines.

RS

Desflurane is a respiratory depressant, causing dose-dependent decreases in tidal volume and an increase in respiratory rate. The drug depresses the ventilatory response to carbon dioxide. Desflurane is markedly irritant to the respiratory tract in concentrations greater than 6%.

CNS

The principal effect of desflurane is general anaesthesia. The drug causes cerebral vasodilation, leading to an increase in cerebral blood flow; the effects on intracranial pressure are unclear. As with other volatile anaesthetic agents, desflurane may increase intracranial pressure in patients with space-occupying lesions. Desflurane decreases cerebral oxygen consumption and is not associated with epileptiform activity. A centrally mediated decrease in skeletal muscle tone results from the use of desflurane.

AS

Desflurane does not decrease hepatic blood flow.

GU

Desflurane does not decrease renal cortical blood flow.

Metabolic/other

Rapid alterations in desflurane concentrations cause transient increases in catecholamine levels.

Toxicity/side effects

There is a high incidence of airway irritation and reactivity during the use of high concentrations of desflurane, making it unsuitable for use during gaseous induction. It is not recommended for induction in children as airway irritation may be severe. Desflurane is a trigger agent for the development of malignant hyperthermia. Desflurane may cause post-operative nausea and vomiting.

Kinetics

Absorption

The major factors affecting the uptake of volatile anaesthetic agents are solubility, cardiac output, and the concentration gradient between the alveoli and venous blood. Due to the low blood/gas partition coefficient of desflurane, it is exceptionally insoluble in blood; alveolar concentration, therefore, reaches inspired concentration very rapidly (fast wash-in rate), resulting in a rapid induction of anaesthesia. An increase in cardiac output increases the rate of alveolar uptake and slows the induction of anaesthesia. The concentration gradient between the alveoli and venous blood approaches zero at equilibrium; a large concentration gradient favours the onset of anaesthesia.

Distribution

The drug is initially distributed to organs with a high blood flow (brain, heart, liver, kidney) and later to less well-perfused organs (muscle, fat, bone).

Metabolism

0.02% of an administered dose is metabolized, predominantly to trifluoroacetic acid.

Excretion

Excretion is via the lungs, predominantly unchanged; trace quantities of trifluoroacetic acid are excreted in the urine. Elimination of desflurane is rapid due to its low solubility, resulting in a fast washout rate. Rapid washout occurs even after prolonged administration of desflurane.

Special points

Desflurane potentiates the action of co-administered depolarizing and non-depolarizing muscle relaxants.

Due to the physical characteristics of desflurane, a specific vaporizer is used to administer the drug. The vaporizer is comprised of an electrically heated vaporization chamber in which desflurane is heated to 39°C at a pressure of 1550 mmHg. A percentage control dial controls the flow of desflurane vapour into the fresh gas flow (1% graduations from 0–10%; 2% graduations from 10–18%). A fixed restriction in the fresh gas flow path and the use of a differential pressure transducer allows the vaporizer to match the pressure of desflurane vapour upstream of the control valve with the pressure of the fresh gas flow at the fixed restriction.

As with other volatile anaesthetic agents, the co-administration of N_2O, benzodiazepines, or opioids lowers the MAC of desflurane.

Desflurane may be used safely in patients breathing spontaneously via a laryngeal mask.

Dexmedetomidine

Uses

Dexmedetomidine is used as a sedative for post-surgical patients requiring mechanical ventilation.

Chemical

An imidazole derivative.

Presentation

As a clear, colourless, isotonic solution containing 100 micrograms/ml of dexmedetomidine base and 9 mg/ml of sodium chloride in water. The solution is preservative-free and contains no additives.

Main action

Sedation, anxiolysis, and analgesia.

Mode of action

Dexmedetomidine is a specific alpha-2 adrenoceptor agonist which acts via post-synaptic alpha-2 receptors to increase conductance through potassium ion channels.

Route of administration/doses

The drug is administered by intravenous infusion, commencing at 1 micrograms/kg for 10 minutes, then at 0.2–0.7 micrograms/kg/hour. The duration of use should not exceed 24 hours. Dexmedetomidine has also been administered transdermally and intramuscularly.

Effects

CVS

The drug causes a predictable decrease in mean arterial pressure and heart rate.

RS

Dexmedetomidine causes a slight increase in $PaCO_2$ and a decrease in minute ventilation with minimal change in respiratory rate—these effects are not clinically significant.

CNS

The drug is sedative and anxiolytic—ventilated patients remain easily rousable and cooperative during treatment. Reversible memory impairment is an additional feature.

Metabolic/other

Dexmedetomidine causes a decrease in plasma adrenaline and noradrenaline concentrations. It does not impair adrenal steroidogenesis when used in the short term.

Toxicity/side effects

Hypotension, bradycardia, nausea, and a dry mouth are the most commonly reported side effects of the drug.

Kinetics

Distribution

Dexmedetomidine is 94% protein-bound in the plasma; the V_D is 1.33 l/kg. The distribution half-life is 6 minutes.

Metabolism

The drug undergoes extensive hepatic metabolism to methyl and glucuronide conjugates.

Excretion

95% of the metabolites are excreted in the urine. The elimination half-life is 2 hours and the clearance is 39 l/hour.

Special points

The drug shows a pharmacodynamic interaction with volatile agents and analgesic agents. The clearance is decreased in hepatic impairment although renal impairment does not significantly alter its pharmacokinetics. Dexmedetomidine is currently licensed for use in the USA, but not Europe.

Dextrans

Uses

Dextrans are used:

1. for plasma volume replacement in haemorrhage, burns, or excessive fluid and electrolyte loss and
2. in the prophylaxis of post-operative thromboembolism.

Chemical

Dextrans are polysaccharide derivatives of sucrose by the action of the bacterium, *Leuconostoc mesenteroides*; the preparation is then further processed by hydrolysis and fractionation.

Presentation

Dextrans are available as Dextran 40 and Dextran 70. Both agents are presented as clear, colourless solutions in either 5% glucose or 0.9% saline. Dextran 40 is a 10% solution containing molecules with an average molecular weight of 40 000. 90% of molecules have a molecular weight within the range 10 000–75 000. Dextran 70 is a 6% solution containing molecules with an average molecular weight of 70 000. 90% of molecules have a molecular weight within the range 20 000–115 000.

Main action

Plasma volume expansion and an anti-thrombotic effect.

Mode of action

Each gram of dextran in the circulation will retain approximately 20 ml of water by its osmotic effect; an infusion of 500 ml of Dextran 40 will maximally increase the circulating plasma volume by approximately 1000 ml. An infusion of 500 ml of Dextran 70 will increase the circulating plasma volume by approximately 750 ml. Molecules above the renal threshold for dextran elimination of 55 000 daltons are generally retained within the intravascular space, whereas those below 20 000 daltons have access to the interstitial space. Dextrans exert their anti-thrombotic action by reducing ADP-induced platelet aggregation and by decreasing the activating effect of thrombin on platelets. These agents also alter fibrinogen binding.

Route of administration/doses

The specific dose of an agent administered is dependent on the clinical indication, the haemodynamic status of the patient, and particular agent being used. When used in the prophylaxis of post-operative thrombosis, the adult dose is 500 ml infused over 4–6 hours in the immediate post-operative period, repeated on the next day. For high-risk cases, this may be continued on alternate days for up to 2 weeks.

Effects

CVS

The haemodynamic effects of dextrans are proportional to the prevailing circulating volume. The duration of action of these agents depends on the type of dextran used.

RS

Dextran 70 appears to protect against the development of ARDS in patients with multiple trauma.

Metabolic/other

Infusion of dextran reduces serum lipid levels and produces a reduction in the serum albumin concentrations.

Toxicity/side effects

Severe hypersensitivity reactions occur in 1 in 3300—this is probably due to a cross-reaction with antibodies to a recent pneumococcal infection. Overtransfusion may lead to pulmonary oedema. Increased capillary oozing due to improved perfusion pressure and capillary flow may be noted perioperatively. Acute renal failure may complicate the use of Dextran 40 when it is used in the management of profound hypovolaemia.

Kinetics

Data are incomplete.

Distribution

Chronic overdosage leads to the storage of dextrans in the liver. Dextrans are not significantly protein-bound.

Metabolism

Occurs by the action of dextranases present in the lung, liver, kidney, and spleen to carbon dioxide and water.

Excretion

Dextran 70 has a half-life of 23–25.5 hours and Dextran 40 has a half-life of 4–9 hours. Small molecules are excreted renally; the remainder are metabolized and excreted as carbon dioxide and water.

Special points

Dextrans do not interfere with cross-matching if enzymatic methods are used (although older preparations did).

If a dextran of molecular weight 1000 is administered prior to the administration of Dextran 40/70, the incidence of anaphylaxis is reduced by 15- to 20-fold.

Diamorphine

Uses

Diamorphine is used:

1. for premedication
2. as an analgesic in the management of moderate to severe pain
3. in the treatment of left ventricular failure
4. as an antitussive agent and
5. to provide analgesia during terminal care.

Chemical

A synthetic diacetylated morphine derivative.

Presentation

As tablets containing 10 mg, and as a lyophilised white powder in ampoules containing 5/10/30/ 100/500 mg of diamorphine hydrochloride for reconstitution with water. A number of non-proprietary elixirs and suppositories are also available.

Main Action

Analgesia, euphoria and respiratory depression.

Mode of Action

Diamorphine is a pro-drug; it does not possess an unsubstituted phenolic hydroxyl group at the 3-position and acts via active derivatives (6-o-acetylmorphine and morphine) which are mu-opioid receptor agonists. Opioids appear to exert their effects by increasing intracellular calcium concentration which, in turn, increases potassium conductance and hyperpolarisation of excitable cell membranes. The decrease in membrane excitability that results may decrease both pre-and post-synaptic responses.

Route of Administration/Dose

The average adult dose by the intravenous or intramuscular route is 5–10 mg. The corresponding intrathecal dose is approximately 250 mcg. An epidural dose is 2.5–5 mg. Due to its higher lipid solubility, the drug has a more rapid onset of action than morphine and has a duration of action of 90 minutes after intramuscular administration.

Effects

CVS

Diamorphine has little effect on the cardiovascular system when used in normal doses. In high doses, it may cause bradycardia due to a combination of increased vagal activity and decreased sympathetic activity; hypotension resulting from a decrease in systemic vascular resistance may occur.

RS

The principal effect of the drug is respiratory depression in opioid-naive subjects, with a decreased ventilatory response to hypoxia and hypercapnia. Diamorphine also has a potent antitussive action. Bronchoconstriction may occur with the use of high doses of the drug.

CNS

Diamorphine is 1.5–2 times as potent an analgesic agent as morphine. The drug tends to cause marked euphoria; there is a clinical impression that it causes less nausea and vomiting than morphine. Miosis is produced as a result of stimulation of the Edinger-Westphal nucleus. Seizures may occur with the use of high doses of the drug.

AS

Diamorphine decreases gastrointestinal motility and decreases gastric acid, biliary and pancreatic secretion; it also increases the common bile duct pressure by causing spasm of the sphincter of Oddi. There is a clinical impression that the drug causes less constipation than does an equipotent dose of morphine.

GU

The drug increases the tone of the ureters, bladder detrusor muscle and sphincter and may precipitate urinary retention.

Metabolic/Other

Mild diaphoresis and piloerection may occur with the use of diamorphine. Intrathecal diamorphine suppresses the metabolic response to surgery.

Toxicity/Side Effects

Respiratory depression, nausea and vomiting, hallucinations and dependence may complicate the use of diamorphine. Pruritus may occur after epidural or spinal administration of the drug.

Kinetics

Data are incomplete due to the instability of the drug in *vivo* and difficulties in assay methodology.

Absorption

Diamorphine is extensively absorbed when administered orally; the bioavailability appears to be low due to an extensive first-pass metabolism,

Distribution

The drug is 40% protein-bound in the plasma; the V_D is 350 l.

Metabolism

Diamorphine undergoes rapid enzymatic hydrolysis in the plasma and in association with red blood cells, probably via pseudocholinesterase and at least three esterases located within red blood cells. The initial metabolic product is 6-0-acetylmorphine (which is the active form of the drug) which is, in turn, further metabolised to morphine, with subsequent glucuronidation.

Excretion

50–60% of an administered dose appears in the urine as a morphine derivative; 0.13% is excreted unchanged. The elim-ination half-life of diamorphine is 3 minutes. The clearance of the morphine component is 3.1 ml/min/kg.

Special Points

Late respiratory depression has not been reported following the use of epidural diamorphine. The actions of the drug are all reversed by naloxone.

Diamorphine is not removed by dialysis.

Diazepam

Uses

Diazepam is used:

1. in the short-term treatment of anxiety
2. in the treatment of status epilepticus
3. muscle spasm in tetanus and other spastic conditions
4. alcohol withdrawal and for
5. premedication and
6. sedation during endoscopy and procedures performed under local anaesthesia.

Chemical

A benzodiazepine.

Presentation

As tablets containing 2/5/10 mg, a syrup containing 0.4 mg/1 mg/ml, as 10 mg suppositories, and as a solution for rectal administration containing 2/4 mg/ml of diazepam. The drug is also supplied as a clear, yellow solution and as a white oil-in-water emulsion for injection containing 5 mg/ml.

Main actions

1. hypnosis
2. sedation
3. anxiolysis
4. anterograde amnesia
5. anticonvulsant and
6. muscular relaxation.

Mode of action

Benzodiazepines are thought to act via specific benzodiazepine receptors found at synapses throughout the central nervous system, but concentrated especially in the cortex and midbrain. Benzodiazepine receptors are closely linked with GABA receptors and appear to facilitate the activity of the latter. Activated GABA receptors open chloride ion channels which then either hyperpolarize or short-circuit the synaptic membrane.

Diazepam has kappa-opioid agonist activity *in vitro*, which may explain the mechanism of benzodiazepine-induced spinal analgesia.

Route of administration/doses

The adult oral dose is 2–60 mg/day in divided doses; the initial intravenous dose is 10–20 mg, increasing according to clinical effect.

Effects

CVS

A transient decrease in blood pressure and a slight decrease in cardiac output may occur following the intravenous administration of diazepam. The coronary blood flow is increased secondary to coronary arterial vasodilation; a decrease in myocardial oxygen consumption has also been reported.

RS

Large doses cause respiratory depression; hypoxic drive is depressed to a greater degree than is hypercarbic drive.

CNS

Diazepam is anxiolytic and decreases aggression although paradoxical excitement may occur. Sedation, hypnosis, and anterograde amnesia occur after the administration of diazepam. The drug has anticonvulsant and analgesic properties and depresses spinal reflexes.

Toxicity/side effects

Depression of the central nervous system, including drowsiness, ataxia, and headache, may complicate the use of diazepam. Rashes, gastrointestinal upsets, and urinary retention have also been reported. Tolerance and dependence may occur with prolonged use of benzodiazepines; acute withdrawal of benzodiazepines in these circumstances may produce insomnia, anxiety, confusion, psychosis, and perceptual disturbances. Intravenous diazepam is highly irritant to veins; the oil-in-water preparation is less so.

Kinetics

Absorption

Diazepam is rapidly absorbed after oral administration; the bioavailability is 86–100%. Absorption after intramuscular administration is slow and erratic.

Distribution

The drug is 99% protein-bound in the plasma; the V_D is 0.8–1.4 l/kg.

Metabolism

Diazepam is converted in the liver to active products; the major metabolite is desmethyldiazepam. Other metabolites are oxazepam (which is further metabolized by glucuronidation) and temazepam. These metabolites are active; desmethyldiazepam has a half-life of 100 hours.

Excretion

The metabolites are excreted in the urine as the oxidized and glucuronide derivatives; less than 1% is excreted unchanged. The clearance is 0.32–0.44 ml/min/kg (this is reduced by 42% by the concurrent administration of halothane) and the elimination half-life is 20–40 hours.

Special points

Diazepam decreases the MAC of volatile agents and potentiates non-depolarizing muscle relaxants. Cimetidine decreases the clearance of co-administered diazepam and thereby increases the plasma levels of the latter. Diazepam is adsorbed onto plastic.

The drug is not removed by dialysis.

Diclofenac

Uses

Diclofenac is used in the treatment of:



1. rheumatoid and osteoarthritis
2. musculoskeletal disorders
3. soft tissue injuries
4. ankylosing spondylitis
5. acute gout
6. renal and biliary colic
7. dysmenorrhoea
8. minor post-surgical pain and as an adjunct to systemic opioid therapy
9. as an antipyretic and
10. to inhibit perioperative miosis and post-operative inflammation in cataract surgery.

Chemical



A phenylacetic acid derivative.

Presentation

As 25/50/100 mg tablets, 12.5/25/50/100 mg suppositories, and in ampoules containing either 25 mg/ml or 75 mg/2ml of diclofenac sodium for injection, depending on the nature of the preparation. An emulsified gel as diethylammonium and eye drops as a 0.1% solution of diclofenac sodium are also available. Modified release/slow release preparations are also available for oral administration in addition to a dispersible formulation. Depending on the intravenous preparation, the following additives may be present: mannitol, sodium metabisulphite, benzyl alcohol, propylene glycol, sodium hydroxide, or hydroxypropylbetadex (a solubilizing agent).

Main actions

Analgesic, anti-inflammatory, and antipyretic.

Mode of action

Diclofenac is a non-specific inhibitor of cyclo-oxygenase (COX-2:COX-1 ratio = 1:1) which converts arachidonic acid to cyclic endoperoxidases, thus preventing the formation of prostaglandins, thromboxanes, and prostacylin. Prostaglandins are involved in the sensitization of peripheral pain receptors to noxious stimuli. The drug may also inhibit the lipo-oxygenase pathway by an action on hydroperoxy fatty acid peroxidase.

Routes of administration/doses

The adult oral dose is 75–150 mg/day in divided doses; the rectal dose is 100 mg, usually administered at night with further suppositories or tablets up to a maximum dose of 150 mg per 24 hours; it may also be given pre- or perioperatively. The intramuscular dose is 75 mg once or twice daily. The paediatric dose is 1 mg/kg three times a day. The intravenous dose is 25–75 mg, up to a maximum daily dose of 150 mg. Depending on the intravenous preparation, a bolus administration may or may not be recommended. Some preparations require dilution in 100–500 ml of 0.9% sodium chloride or 5% glucose solutions with subsequent buffering with sodium bicarbonate solution.

Effects

AS

Diclofenac causes less gastrointestinal damage than aspirin or indometacin. Dyspepsia, nausea, bleeding from gastric and duodenal vessels, mucosal ulceration, perforation, and diarrhoea are expected COX-1 effects. The drug may lead to disease exacerbation in patients with Crohn's disease or ulcerative colitis. Diclofenac may cause a rise in ALT in up to 15% of patients.

RS

Bronchoconstriction and eosinophilia may occur in up to 20% of asthmatic patients.

GU

The plasma renin activity and aldosterone concentrations are reduced by 60–70%.

Metabolic/other

Diclofenac interferes with neutrophil function. The drug reversibly inhibits platelet aggregation, but does not affect bleeding time, prothrombin time, plasma fibrinogen, or factors V and VII to XIII. Osteoblast activity is inhibited in animal studies and *in vitro*.

Toxicity/side effects

Occur in 12%; complications are related to the duration of therapy and risks increase markedly after more than 5 days of continuous therapy, especially in the elderly.

Disturbances of the gastrointestinal and central nervous system occur occasionally.

Rashes, hepatic, renal, and haematological impairment have been reported.

As with other NSAIDs, prolonged use may lead to analgesic nephropathy characterized by papillary necrosis and interstitial fibrosis. Acute renal failure may be precipitated when NSAIDs are administered to patients who have renal perfusion dependent on prostaglandin production (i.e. when there are high levels of circulating vasoconstrictors or hypovolaemia).

Intramuscular injection may be painful and sterile abscesses have been reported.

The drug may inhibit uterine contraction.

Kinetics

Absorption

The drug is well absorbed when administered by all routes. The oral bioavailability is 60%.

Distribution

Diclofenac is 99.5% protein-bound in the plasma, predominantly to albumin. The V_D is 0.12–0.17 l/kg. The drug crosses the placenta in animal models. Diclofenac enters synovial fluid and reaches maximum concentration 2–4 hours after peak plasma concentrations have been achieved. Drug levels within the synovial fluid may remain high for up to 12 hours before being eliminated with a half-life of 3–6 hours.

Metabolism

Diclofenac undergoes significant first-pass metabolism, principally in the liver by hydroxylation and methoxylation to phenolic metabolites with subsequent conjugation to inactive glucuronide and sulphate metabolites. Two phenolic metabolites have biological activity although much reduced compared with the parent drug.

Excretion

Approximately 65% of the dose is excreted in the urine and 35% in the bile. Less than 1% is excreted unchanged. The clearance is 263 ml/min and the terminal elimination half-life in plasma is 1–2 hours.

Special points

Renal and hepatic impairment have little effect on the plasma concentration of diclofenac. The drug may increase plasma concentrations of co-administered digoxin and lithium by reducing renal clearance.

Diclofenac may increase the effect of co-administered oral anticoagulants, heparin, and sulphonylureas due to displacement from plasma proteins.

NSAIDs antagonize the antihypertensive effects of ACE inhibitors via the inhibition of vasodilatory prostaglandin synthesis. The risk of renal impairment increases if NSAIDs and ACE inhibitors are co-administered. NSAIDs inhibit the activity of diuretics.

Diclofenac should not be administered to aspirin-sensitive asthmatics.

In patients with severe renal impairment, the excipient hydroxypropylbetadex is subject to renal elimination and may accumulate if present in the intravenous preparation. The clinical relevance of this in man is unclear.

NSAIDs cause closure of the ductus arteriosus in the fetus.

Digoxin

Uses

Digoxin is used in the treatment of:

1. atrial fibrillation and flutter
2. heart failure and may be of use
3. in the prevention of supraventricular dysrhythmias following thoracotomy.

Chemical

A glycoside (sterol lactone and a sugar).

Presentation

As 0.0625/0.125/0.25 mg tablets, an elixir containing 0.05 mg/ml, and as a clear, colourless solution for injection containing 0.25 mg/ml of digoxin.

Main action

Positive inotropism and slowing of the ventricular response.

Mode of action

Digoxin acts both directly and indirectly; its direct action is exerted by binding to and inhibiting the action of Na^+K^+ATPase within the sarcolemma cell membrane. This produces an increase in the intracellular sodium ion concentration and a decrease in intracellular potassium ion concentration. The increase in intracellular sodium ion concentration causes displacement of bound intracellular calcium ions. This increased availability of calcium ions results in a positive inotropic action. The decrease in intracellular potassium ion concentration leads to slowing of atrio-ventricular conduction and of the pacemaker cells. The drug also acts indirectly by modifying autonomic activity and increasing efferent vagal activity.

Route of administration/doses

The loading dose by both oral and parenteral routes is 10–20 micrograms/kg 6-hourly until the desired effect is achieved. Intravenous injection must be slow (at a rate not exceeding 0.025 mg/min)—the peak effects are observed 2 hours after intravenous administration. The maintenance dose is 10–20 micrograms/kg/day in divided doses; therapy should be adjusted according to response, guided (where appropriate) by measurement of serum levels of the drug. The therapeutic range is 1–2 micrograms/ml.

Effects

CVS

The main action of digoxin is to increase the force of cardiac contraction; automaticity and contractility also increase. The heart rate is slowed due to a combination of improved haemodynamics, depression of sinus node discharge, slowing of atrio-ventricular nodal conduction, an increase in the atrio-ventricular nodal refractory period, and an indirect vagotonic effect. Rapid intravenous administration of digoxin may cause vasoconstriction, leading to hypertension and decreased coronary blood flow. The characteristic ECG changes produced by the drug include prolongation of the PR interval, ST segment depression, T wave flattening, and shortening of the QT interval.

GU

Digoxin has a mild intrinsic diuretic effect.

Toxicity/side effects

Side effects are common with digoxin, especially if the therapeutic range is exceeded. The gastrointestinal side effects include anorexia, nausea and vomiting, diarrhoea, and abdominal pain. The neurological side effects of the drug include headache, drowsiness, confusion, visual disturbances, muscular weakness, and coma. Digoxin may cause any form of dysrhythmia, especially junctional bradycardia, ventricular bigemini, and second- or third-degree heart block. Rashes and gynaecomastia occur uncommonly. Digoxin-specific antibody fragments are available for the treatment of digoxin toxicity.

Kinetics

Absorption

Absorption from the gastrointestinal tract is highly variable and the bioavailability by this route varies from 60–90%. Absorption after intramuscular injection is erratic.

Distribution

Digoxin is 20–30% protein-bound in the plasma; the V_D is 5–11 l/kg. The concentrations achieved at steady state in cardiac tissue are 15–30 times that of plasma.

Metabolism

Less than 10% of the dose undergoes hepatic metabolism via stepwise cleavage of the sugar moieties.

Excretion

50–70% of an administered dose of digoxin is excreted unchanged in the urine as a result of glomerular filtration and active tubular secretion. The clearance is dependent on renal function and may be calculated from the formula:

Clearance = (0.88 x creatinine clearance + 0.33) ± 52%

The elimination half-life is 1.6 days. The dose interval should be increased in the presence of renal impairment.

Special points

Patients receiving suxamethonium, pancuronium, or beta-adrenergic agonists concurrently with digoxin may exhibit an increased incidence of dysrhythmias.

The following states increase the likelihood of digoxin toxicity: hypokalaemia, hypernatraemia, hypercalcaemia, hypomagnesaemia, acid-base disturbances, hypoxaemia, and renal failure. Co-administered verapamil, nifedipine, amiodarone, and diazepam also increase plasma digoxin concentrations.

Digoxin is not removed by dialysis.

Diltiazem

Uses

Diltiazem is recommended for use:

1. in the treatment of stable and variant angina and may be of use in the treatment of:
2. hypertension
3. supraventricular tachycardias
4. Raynaud's phenomenon
5. migraine and
6. oesophageal motility disorders.

Chemical

A benzothiapine.

Presentation

As 60/90/120/180/240/300 mg tablets of diltiazem hydrochloride.

Main action

Diltiazem increases myocardial oxygen supply and decreases myocardial oxygen demand by coronary artery dilation, possibly aided by direct and indirect haemodynamic alterations.

Mode of action

Diltiazem acts via dose-dependent inhibition of the slow inward calcium current in normal cardiac tissue.

Route of administration/doses

The adult oral dose is 30–120 mg 6–8-hourly.

Effects

CVS

Diltiazem is a potent peripheral and coronary arterial vasodilator, leading to a decrease in the systemic and pulmonary vascular resistances; the cardiac output increases due to a reduction in afterload. Little effect on the heart rate occurs in man; bradycardia tends to occur with chronic use. A–V nodal conduction is decreased by the drug; diltiazem is thus of use in the treatment of supraventricular tachycardias.

RS

The drug inhibits bronchoconstriction due to inhaled histamine in man.

AS

A significant reduction in lower oesophageal pressure is produced in patients with achalasia although no effect is seen in normal subjects.

GU

Renal artery dilation, leading to an increased renal plasma flow and subsequent diuresis, occurs after the administration of diltiazem. Uterine activity is decreased *in vitro*.

Metabolic/other

Platelet aggregation is decreased by diltiazem *in vitro* although no significant effect on haemostasis can be demonstrated *in vivo*.

Toxicity/side effects

Occur in 2–10% and include headaches, flushing, peripheral oedema, and bradycardia.

Kinetics

Absorption

90% of an oral dose is absorbed; the bioavailability by this route is 33–40% due to a significant first effect.

Distribution

Diltiazem is 78–87% protein-bound in the plasma; the V_D is 5.3 l/kg.

Metabolism

Occurs by deacetylation and demethylation in the liver with subsequent conjugation to glucuronide and sulphates—the metabolites are active.

Excretion

1–4% is excreted unchanged in the urine. The clearance is 11.5–21.3 ml/kg/min and the elimination half-life is 2–7 hours. Renal failure has no effect on the pharmacokinetics of diltiazem.

Special points

Caution should be used if the drug is administered concurrently with a beta-adrenergic antagonist as serious bradycardias may arise. All volatile agents in current use decrease calcium ion release from the sarcoplasmic reticulum and decrease calcium ion flux into cardiac cells; the negative inotropic effects of diltiazem are thus additive with those of the volatile agents. Experiments in animals have demonstrated an increased risk of sinus arrest if volatile agents and calcium antagonists are used concurrently. If withdrawn acutely (especially in the post-operative period) after chronic oral use, severe rebound hypertension may result. Calcium antagonists may also:

1. reduce the MAC of volatile agents by up to 20% and
2. increase the efficacy of neuromuscular blocking agents. Diltiazem may increase the plasma concentration of co-administered digoxin by 20–60%. It also increases the toxicity of bupivacaine in animal models.

Dobutamine

Uses

Dobutamine is used to provide inotropic support in patients with a low cardiac output secondary to:

1. myocardial infarction
2. cardiac surgery
3. cardiomyopathy
4. positive end expiratory pressure ventilation
5. in septic shock to increase oxygen transport to the tissues and
6. cardiac stress testing.

Chemical

A synthetic isoprenaline derivative.

Presentation

Dobutamine is presented in vials which hold a solution for injection containing 12.5/50 mg/ml of dobutamine hydrochloride, which needs to be diluted prior to infusion.

Main action

Positive inotrope.

Mode of action

Dobutamine acts directly on catecholamine receptors to activate adenyl cyclase, which catalyzes the conversion of ATP to cAMP. This results in increased cell membrane permeability to calcium ions which are necessary for depolarization and completion of the contractile process.

Route of administration/doses

Dobutamine is infused intravenously, diluted in a suitable crystalloid to a volume of at least 50 ml. The dose range is 0.5–40 micrograms/kg/min, titrated against response; the drug acts within 1–2 minutes. Solutions should be used within 24 hours.

Effects

CVS

The primary action of dobutamine is to increase cardiac contractility by a direct action on cardiac beta-1 adrenoceptors. Sinoatrial nodal automaticity is increased, leading to an increased heart rate; atrio-ventricular nodal conduction velocity is also increased by the drug. Dobutamine also has activity at alpha- and beta-2 adrenoceptors and thus tends to have only moderate effect on the systemic vascular resistance. Myocardial perfusion may increase. The drug leads to a decrease in both the left ventricular end-diastolic pressure and the systemic vascular resistance and thus to an increase in cardiac index in patients with severe congestive cardiac failure.

CNS

Stimulation occurs at high-dose ranges.

GU

The urine output increases secondary to an increase in cardiac output; dobutamine is devoid of any specific renal vasodilatory effect.

Metabolic/other

Dobutamine enhances natural killer cell activity. It decreases blood glucose and increases free fatty acid concentrations.

Toxicity/side effects

Are uncommon at dose ranges below 10 micrograms/kg/min. Dysrhythmias, excessive tachycardia and hypertension, fatigue, nervousness, headache, and chest pain may occur. Allergic phenomena have been reported.

Kinetics

Distribution

Due to a half-life of 2 minutes, steady state concentrations occur within 8–10 minutes when the drug is given at a fixed rate. The V_D is 0.2 l/kg.

Metabolism

The major route of metabolism is by methylation via catechol-O-methyl transferase to 3-O-methyldobutamine with subsequent conjugation to glucuronide.

Excretion

The (inactive) 3-O-methyl derivative is excreted in the urine with 20% of the total dose appearing in the faeces. The clearance is 244 l/hour and the elimination half-life is 2 minutes.

Special points

Dobutamine should not be used in patients with cardiac outflow obstruction, e.g. cardiac tamponade or aortic stenosis. Tachyphylaxis may occur during prolonged infusion.

Domperidone

Uses

Domperidone is used for the symptomatic treatment of nausea and vomiting from any cause.

Chemical

A butyrophenone derivative.

Presentation

As tablets containing l0 mg and a suspension containing 1 mg/ml of domperidone; 30 mg suppositories are also available.

Main action

Increased gastrointestinal motility and tone, and a central antiemetic effect.

Mode of action

The effects of domperidone on gastrointestinal mobility appear to be mediated by antagonism of peripheral dopaminergic (D2) receptors. Little else is known of the mechanism of action of the drug.

Route of administration/doses

The adult oral dose is 10–20 mg and the rectal dose 60 mg 4–8-hourly.

Effects

CVS

Domperidone has no significant effects on cardiac output, heart rate, blood pressure, or conduction.

CNS

The drug does not readily cross the blood–brain barrier and is thus essentially devoid of central effects.

AS

The drug increases lower oesophageal sphincter tone and the rate of gastric emptying. It has an antiemetic effect indistinguishable from that of metoclopramide in the prevention of post-operative vomiting, but appears to be more effective in the treatment of established post-operative vomiting.

Metabolic/other

The drug causes an increase in the serum prolactin concentration.

Toxicity/side effects

Domperidone is generally very well tolerated; there are occasional reports of extrapyramidal reactions occurring with the use of the drug. Galactorrhoea and gynaecomastia have also been reported.

Kinetics

Absorption

The bioavailability is 13–17% when administered orally due to first-pass metabolism in the gut wall and liver.

Distribution

Domperidone is 92% protein-bound in the plasma; the V_D is 5.7 l/kg.

Metabolism

90% of the drug is metabolized by hydroxylation and oxidative N-dealkylation.

Excretion

30% appears in the urine and 60% in the faeces; the elimination half-life is 7.5 hours. Accumulation appears not to occur in the presence of renal impairment.

Special points

Cardiac arrest has been reported after the rapid intravenous administration of domperidone. This preparation is no longer available.

Dopamine

Uses

Dopamine has been used in the management of:

1. low cardiac output states
2. septicaemic shock and
3. impending renal failure to promote diuresis.

Chemical

A naturally occurring catecholamine.

Presentation

As a clear, colourless solution for injection containing 40/160 mg/ml of dopamine hydrochloride.

Main action

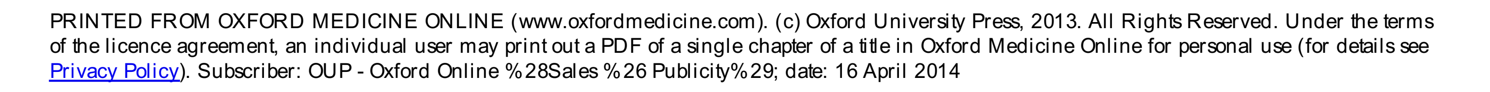
Sympathomimetic and increased renal blood flow.

Mode of action

In low doses (1–5 micrograms/kg/min), dopamine acts upon specific dopaminergic receptors, of which at least two types are recognized. D1 receptors are a form of adenyl cyclase; D2 receptors are not linked to adenyl cyclase and are involved in the central modulation of behaviour and movement. At higher dose ranges, the drug acts via direct and indirect stimulation of beta- and alpha-adrenergic receptors; at an infusion rate of 5–10 micrograms/kg/min, beta-stimulation predominates whereas at infusion rates exceeding 15 micrograms/kg/min, alpha effects predominate.

Route of administration/doses

Dopamine is administered by intravenous infusion, diluted in glucose/saline or Hartmann's solution. A dedicated central vein is preferred for the administration of the drug. A dose of 1–20 micrograms/kg/min may be used, titrated according to response. The drug acts within 5 minutes and has duration of action of 10 minutes.



Effects

CVS

The cardiovascular effects of dopamine depend upon the rate of infusion. At low doses (5 micrograms/kg/min), beta-adrenergic effects predominate, leading to a positive inotropic effect, increased automaticity, and an increase in cardiac output and coronary blood flow; the drug has little effect on heart rate. Systolic and diastolic blood pressures may decrease slightly due to a decrease in the systemic vascular resistance (a beta-2 effect). With the use of high doses (15 micrograms/kg/min), peripheral vasoconstriction (an alpha-adrenergic effect) occurs, leading to an increased venous return and systolic blood pressure. Dopamine has variable effects on the pulmonary vascular resistance.

RS

Dopamine activates the carotid bodies and may decrease the ventilatory response to hypoxia.

CNS

Dopamine is a central neurotransmitter involved in the modulation of movement; exogenous dopamine does not cross the blood–brain barrier except in its laevorotatory form. The drug causes marked nausea due to a direct action on the chemosensitive trigger zone (which lies outside the blood–brain barrier). Increased intraocular pressure occurs with dopamine administration in critically ill patients.

AS

The drug causes vasodilation of the splanchnic circulation by an effect on dopaminergic receptors and decreases gastroduodenal motility in the critically ill.

GU

In low doses (1–5 micrograms/kg/min), dopamine causes a marked decrease in the renal vascular resistance with a corresponding increase in renal blood flow. Dopamine produces diuresis via the D1 receptors on the luminal and basal membranes of the proximal convoluted tubule. Natriuresis is produced by the inhibition of Na^+K^+ATPase. Creatinine clearance remains unaltered.

Metabolic/other

Dopamine reduces the release of prolactin and aldosterone. The drug appears to induce or aggravate the sick euthyroid syndrome and partial hypopituitarism and also depresses growth hormone secretion in the critically ill.

Toxicity/side effects

Tachycardia, dysrhythmias, angina, hypertension, and nausea and vomiting may all follow the administration of the drug. Extravasation of dopamine may cause ischaemic tissue necrosis and skin sloughing. An increase in perioperative cardiac events may occur.

Kinetics

Absorption

Dopamine is ineffective when administered orally.

Metabolism

Exogenous dopamine is metabolized in the plasma, liver, and kidneys by monoamine oxidase and catechol-O-methyltransferase to homovanillic acid and 3,4-dihydroxyphenylacetic acid. 25% of an administered dose is converted to noradrenaline within adrenergic nerve terminals.

Excretion

Occurs principally in the urine as homovanillic acid and its sulphate and glucuronide derivatives; a small fraction is excreted unchanged. The clearance is 234–330 l/hour and the elimination half-life is 2 minutes.

Special points

As with all inotropes, correction of hypovolaemia should be ensured before use of the drug. A reduced dose should be used in patients who have recently received MAOIs. Halogenated volatile anaesthetic agents may increase the likelihood of dysrhythmias occurring during the concurrent use of dopamine. The dopaminergic stimulation is blocked by phenothiazines.

There is no evidence dopamine provides renal protection and it may worsen renal ischaemia. It does not prevent the need for renal support nor does it delay the time for support.

The drug is inactivated by alkaline solutions (e.g. sodium bicarbonate).

Dopexamine

Uses

Dopexamine is used in the treatment of:

1. low cardiac output states (including those complicating cardiac surgery)
2. acute heart failure
3. to increase splanchnic blood flow and
4. prevent renal shutdown.

Chemical

A synthetic dopamine analogue.

Presentation

As a clear solution containing 10 mg/ml of dopexamine hydrochloride; the solution should be discarded if it becomes discoloured.

Main action

Arterial vasodilatation, positive inotropism, and renal arterial vasodilatation.

Mode of action

Dopexamine is an agonist at dopaminergic, D1 and D2, receptors and thus leads to relaxation of vascular smooth muscle in the renal, mesenteric, cerebral, and coronary arterial beds (D1 effects) and stimulation of sympathetic pre-junctional receptors, thereby decreasing noradrenaline release (a D2 effect). The drug also inhibits uptake-1 of noradrenaline and has potent beta-2 adrenergic agonist activity.

Routes of administration/doses

Dopexamine should be diluted prior to administration in either glucose or saline and administered via a central vein using a controlled infusion device. The initial dose is 0.5 micrograms/kg/min which may be increased as necessary to a maximum dose of 6 micrograms/kg/min.

Effects

CVS

Dopexamine has positive inotropic and chronotropic effects, and thus increases cardiac output. The drug causes arteriolar vasodilation, leading to a mild decrease in diastolic blood pressure with a slight increase in systolic blood pressure; the left and right ventricular afterload, left ventricular end-diastolic pressure, and pulmonary artery pressure decrease following the administration of the drug. Dopexamine also causes a slight increase in coronary artery blood flow with no attendant alteration in myocardial oxygen extraction. The drug has a low propensity to cause dysrhythmias.

RS

Dopexamine causes measurable bronchodilatation.

CNS

The drug increases the cerebral blood flow secondary to cerebral vasodilation. Nausea and vomiting may result from a weak D2 effect at the chemoreceptor trigger zone.

AS

Splanchnic blood flow may increase due to mesenteric vasodilation.

GU

Dopexamine reduces renal vascular resistance, leading to an increase in renal plasma flow and an attendant diuresis and natriuresis.

Metabolic/other

Beta-2 adrenergic stimulation may result in hypokalaemia and hyperglycaemia; the platelet count may also decrease due to temporary splenic sequestration of platelets.

Toxicity/side effects

The use of the drug may be complicated by headache, flushing, tremor, angina, and dysrhythmias.

Kinetics

Data are incomplete.

Distribution

Dopexamine is 40% bound to red blood cells; the V_D is 317–446 ml/kg.

Metabolism

The drug is rapidly cleared from blood by tissue uptake and is extensively metabolized by methylation and sulphate conjugation.

Excretion

Dopexamine is excreted as metabolites in the urine and faeces; the clearance is 30–35 ml/min/kg and the elimination half-life is 5–10 minutes.

Special points

The use of dopexamine should be avoided in patients with uncorrected hypovolaemia, aortic stenosis, hypertrophic obstructive cardiomyopathy, or a phaeochromocytoma.

Dopexamine has an unexpected antioxidant effect.

Doxapram

Uses

Doxapram is used:

1. as a respiratory stimulant for the treatment of post-operative respiratory depression and acute-on-chronic respiratory failure and has been used
2. in the treatment of laryngospasm
3. to facilitate blind nasal intubation and

4. in the treatment of post-operative shivering.

Chemical

A monohydrated pyrrolidinone derivative.

Presentation

As a clear, colourless solution containing 20 mg/ml and as a solution for infusion containing 2 mg/ml in 5% glucose of doxapram hydrochloride.

Main action

Respiratory stimulation.

Mode of action

Doxapram acts primarily by stimulating the peripheral chemoreceptors and secondarily by a direct action on the respiratory centre.

Routes of administration/doses

The drug may be administered intravenously as a bolus of 1 mg/kg or as an infusion of 1.5–4 mg/min. Given intravenously, doxapram acts in 20–40 seconds; its peak effect is seen at 1–2 minutes and the duration of action is 5–12 minutes, although pharmacological effects are detectable for 2 hours.

Effects

CVS

Doxapram causes an increase in the cardiac output due primarily to an increase in the stroke volume. A slight increase in the blood pressure and heart rate may be produced by the drug.

RS

The minute volume is increased by doxapram due to an increase in the tidal volume; at higher doses, an increase in respiratory rate occurs. The carbon dioxide response curve is displaced to the left by the drug. The work of breathing is increased.

CNS

The cerebral blood flow is increased following the administration of doxapram; the drug has less convulsant activity than other analeptic agents.

AS

In animals, salivation and gastrointestinal tone and motility are increased by the drug.

GU

In animal models, doxapram increases both the urine output and motility within the genitourinary system.

Metabolic/other

Catecholamine and steroid secretion are increased in animal models. The metabolic rate may increase by up to 30% and may lead to hypoxia due to increased oxygen consumption.

Toxicity/side effects

Restlessness, dizziness, hallucinations, excessive sweating, and a sensation of perineal warmth have been described subsequent to the administration of doxapram.

Kinetics

Data are incomplete.

Distribution

The V_D is 1.5 l/kg.

Metabolism

The metabolic pathway of doxapram in man is unknown.

Excretion

5% is excreted unchanged in the urine. The clearance is 370 ml/min and the half-life is 2–4 hours.

Special points

Doxapram has been shown:

1. to lead to a more rapid return to consciousness after inhalational anaesthesia
2. to reverse opioid-induced respiratory depression without reversing analgesia and
3. to prevent the necessity for mechanical ventilation in some patients.

The drug may possibly decrease the incidence of post-operative chest infections.

Oxygen must be given to patients receiving doxapram due to the increased metabolic rate and the increase in the work of breathing.

Droperidol

Uses

Droperidol is used:

1. in premedication
2. in the technique of neuroleptanalgesia
3. in the treatment of nausea and vomiting occurring post-operatively or as a result of chemotherapy
4. in the treatment of psychosis and has been used
5. for the control of perioperative hiccuping.



Chemical

A butyrophenone derivative.

Presentation

As 10 mg tablets, a syrup containing 1 mg/ml, and as a clear solution for injection containing 5 mg/ml of droperidol.

Main action

Antiemetic and neuroleptic.

Mode of action

The antiemetic and neuroleptic effects of the drug appear to be mediated by:

1. central dopaminergic (D2) blockade, leading to an increased threshold for vomiting at the chemoreceptor trigger zone and
2. post-synaptic GABA antagonism.

Routes of administration/doses

The adult oral or intramuscular dose is 5–10 mg and the intravenous dose when used as a neuroleptic agent is 5–15 mg, although the drug appears to be an effective antiemetic in doses as low as 0.5 mg. The onset of action after intravenous administration is 3–20 minutes and the drug may act for up to 12 hours.

Effects

CVS

Droperidol has minimal cardiovascular effects, but its antagonistic effects at alpha-adrenergic receptors may lead to hypotension in the presence of hypovolaemia.

RS

The drug causes small decreases in minute volume, functional residual capacity, and airways resistance.

CNS

Droperidol induces neurolepsis, a state characterized by diminished motor activity, anxiolysis, and indifference to the external environment. The seizure threshold is raised by the drug.

AS

The drug has a powerful antiemetic effect via a central effect at the chemosensitive trigger zone.

Metabolic/other

Droperidol, in common with other dopamine antagonists, may cause hyperprolactinaemia. The drug reduces total body oxygen consumption.

Toxicity/side effects

Extrapyramidal effects occur in 1%. Gastrointestinal disturbances, abnormalities of liver function tests, and allergic phenomena have been reported after the use of droperidol. Malignant neuroleptic syndrome may be precipitated by droperidol.

Kinetics

Absorption

The drug is well absorbed after intramuscular administration. The pharmacokinetics of droperidol after oral administration has not been elucidated.

Distribution

The drug is 85–90% protein-bound in the plasma; the V_D is 1.54–2.54 l/kg.

Metabolism

Droperidol is extensively metabolized in the liver (the major metabolic pathway in animals being oxidative N-dealkylation); the only metabolite that has been identified in man is 2-benzimidazolinone.

Excretion

75% of the dose is excreted in the urine (1% unchanged) and 22% in the faeces. The clearance is 9.7–18.5 ml/min/kg and the elimination half-life is 2–2.5 hours.

Special points

Droperidol is pharmaceutically incompatible with thiopental and methohexital. The sedative effects of the drug are additive with those of other central nervous system depressants administered concurrently.

Drotrecogin

Uses

Drotrecogin alfa is used in the treatment of adult patients with severe sepsis and evidence of dysfunction of more than one organ system.

Chemical

A recombinant version of endogenous activated protein C (APC).

Presentation

As a white to off-white, lyophilized powder in vials containing 5/20 mg of drotrecogin alfa. Each 5 mg vial contains 17 mg of sodium and each 20 mg vial contains 68 mg of sodium.

Main action

The drug acts as an antithrombotic and profibrinolytic agent.

Mode of action

APC is an important regulator of coagulation. In severe sepsis, thrombomodulin expression is markedly reduced, leading to an inefficient anticoagulation regulation via APC with subsequent upregulation of tissue factor and von Willebrand factor and consequent coagulation and DIC. Recombinant APC replaces physiological APC, leading to reduced clot formation.

Route of administration/doses

The drug is administered by continuous intravenous infusion at a dose of 24 micrograms/kg/hour for 96 hours. Initiation of treatment is recommended to occur within 24 hours after the onset of severe sepsis.

Effects

Metabolic/other

The primary action of APC is its anticoagulant effect. In addition, the drug may also lead to inhibition of nitric oxide-induced vascular dysfunction, neutrophil activation, and lymphocyte apoptosis. Following administration of the drug, interleukin-6 levels may fall more rapidly in patients with severe sepsis.

Toxicity/side effects

Administration of the drug increases the risk of bleeding. The risk of a serious bleeding event may be up to 10%.

Kinetics

Distribution

Following administration of the drug by continuous infusion, a steady state is reached with 2 hours of commencement of the infusion.

Metabolism

APC is inactivated by endogenous plasma protease inhibitors. The mechanism by which they are cleared from the plasma is currently unknown.

Excretion

Following discontinuation of an infusion, the drug is rapidly cleared from the plasma in a biphasic manner. The initial alpha-phase is rapid (half-life=13 minutes) followed by a slower beta-phase (half-life=1.6 hours). Clearance of the drug is reduced in the presence of severe renal or hepatic impairment although no dose adjustment is required.

Special points

Drotrecogin alfa (activated) has a minimal effect on the prothrombin time, but may affect APTT laboratory assays.

The drug is contraindicated in the following situations: active internal bleeding, patients with intracranial pathology, concurrent heparin therapy (≥15 IU/kg/hour), known coagulopathy (other than that associated with sepsis), chronic severe hepatic disease, platelet count <30 000 × 10^6/l, and patients at increased risk of haemorrhage (such as those with a history of gastrointestinal haemorrhage, major surgery within 12 hours of drug administration, severe head trauma requiring hospitalization within the last 3 months, patients who have received or who are likely to receive epidural or intrathecal catheter insertion).

The drug is not approved for use in patients with single organ dysfunction. The drug is not approved for use in paediatric patients.




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Drugs in Anaesthesia and Intensive Care (4 ed.)

Susan Smith, Edward Scarth, and Martin Sasada



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Fentanyl

Uses

Fentanyl is used:

1. to provide the analgesic component in general anaesthesia
2. in combination with a major tranquilizer to produce neuroleptanalgesia
3. to provide analgesia during labour when regional anaesthesia is not in use
4. as an agent used for patient-controlled analgesia
5. in premedication and
6. for palliative care.



Chemical

A tertiary amine which is a synthetic phenylpiperidine derivative.

Presentation

As a clear, colourless solution for injection containing 50 micrograms/ml fentanyl citrate; as transdermal patches which deliver 12/25/50/ 75/100 micrograms/hour over a 72-hour period; as sublingual tablets containing 100/200/400/600/800 micrograms; as lozenges containing 200/400/600/800/1200/1600 micrograms; and as fentanyl hydrochloride in an iontophoretic transdermal system. The pKa of fentanyl is 8.4, is 9% unionized at a pH of 7.4, has a molecular weight of 286, and is highly lipid-soluble, having an octanol-water partition coefficient of 717.

Main actions

Analgesia and respiratory depression.

Mode of action

Fentanyl is a highly selective mu-agonist (or MOP agonist); the mu-opioid receptor (MOP receptor) appears to be specifically involved in the mediation of analgesia. Opioids appear to exert their effects by interacting with pre-synaptic Gi-protein receptors, leading to hyperpolarization of the cell membrane by increasing K^+ conductance. Inhibition of adenylate cyclase, leading to reduced production of cyclic adenosine monophosphate, and closure of voltage-sensitive calcium channels also occurs. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routes of administration/doses

The adult dose for premedication by the intramuscular route is 50–100 micrograms. For the induction or supplementation of general anaesthesia, an intravenous dose of 1–100 micrograms/kg may be used. The drug may be administered by intravenous infusion. Fentanyl may also be administered via the epidural route; a dose of 50–100 micrograms is usually employed; or via the spinal route at doses of 5–25 micrograms. The drug acts rapidly in 2–5 minutes due to its high lipid solubility when administered intravenously; a small dose has a duration of action of 30–60 minutes whereas high (>50 micrograms/kg) doses may be effective for 4–6 hours. Following application of a transdermal patch, serum fentanyl concentrations only increase gradually, equilibrium occurring at between 12 and 24 hours. Transdermal fentanyl patches should be replaced every 72 hours whilst iontophoretic transdermal system devices should be replaced or stopped after 24 hours. Administration of fentanyl reduces the amount of hypnotic/volatile agent required to maintain anaesthesia.

Effects

CVS

The most significant cardiovascular effect of fentanyl is bradycardia of vagal origin; cardiac output, mean arterial pressure, pulmonary and systemic vascular resistance, and pulmonary capillary wedge pressure are unaffected by the administration of the drug. Fentanyl obtunds the cardiovascular responses to laryngoscopy and intubation.

RS

Fentanyl is a potent respiratory depressant, causing a decrease in both the respiratory rate and tidal volume; it also diminishes the ventilatory response to hypoxia and hypercarbia. The drug is a potent antitussive agent. Chest wall rigidity (the 'wooden chest' phenomenon) may occur after the administration of fentanyl—this may be an effect of the drug on mu-receptors located on GABA-ergic interneurons. Fentanyl causes minimal histamine release; bronchospasm is thus rarely produced by the drug.

CNS

Fentanyl is 50 to 80 times more potent an analgesic than morphine and has little hypnotic or sedative activity. Miosis is produced as a result of stimulation of the Edinger–Westphal nucleus. There have been several reports of seizure-like motor activity occurring in patients receiving fentanyl; however, no epileptic spike-wave patterns are demonstrable on the EEG (although beta activity is initially decreased and alpha activity is increased; subsequently alpha activity disappears and delta activity predominates).

AS

The drug decreases gastrointestinal motility and decreases gastric acid secretion; it also doubles the common bile duct pressure by causing spasm of the sphincter of Oddi.

GU

Fentanyl increases the tone of the ureters, bladder detrusor muscle, and vesicular sphincter.

Metabolic/other

High doses of fentanyl will obtund the metabolic 'stress response' to surgery although the drug has no effect on white cell function. Unlike morphine, fentanyl does not increase the activity of antidiuretic hormone.

Toxicity/side effects

Respiratory depression may occur post-operatively, possibly related to the appearance of a secondary peak in the plasma fentanyl concentration due to elution from muscle. Nausea, vomiting, and dependence may also complicate the use of the drug.

Kinetics

There is large inter-individual variability in pharmacokinetics.

Absorption

Fentanyl is absorbed orally and has a bioavailability of 33%. Orally administered fentanyl may become highly ionized in the stomach (99.9%), leading to slow absorption in the alkaline small bowel and subsequent first-pass metabolism. Transdermal delivery produces 47% absorption at 24 hours, 88% at 48 hours, and 94% by 72 hours. Drug delivery continues after patch removal.

Distribution

Fentanyl is 81–94% bound to plasma proteins; the V_D is 0.88–4.41 l/kg. The short duration of action of a single dose of the drug is due to redistribution (cf. thiopental) whereas continuous administration leads to saturation of tissues and a significantly prolonged duration of action. Fentanyl is more lipid-soluble than morphine and thus crosses the blood–brain barrier more easily; it thus has a more rapid onset of action than morphine. Additionally, intrathecal fentanyl dose not cause delayed respiratory depression, unlike morphine, as due to its high lipid solubility, it is rapidly absorbed into the spinal cord.

Metabolism

Fentanyl appears to be metabolized primarily by N-dealkylation to norfentanyl with subsequent hydroxylation of this and the parent compound to hydroxypropionyl derivatives. The drug may also undergo hydroxylation and amide hydrolysis. Cytochrome P450 3A4 plays the predominant role in fentanyl metabolism. As well as the liver, this is also found in human intestine. Some enterosystemic cycling of the drug may occur as dose first-pass metabolism (see above). The metabolites are not pharmacologically active.

Excretion

10% of an administered dose is excreted in the urine. The clearance of fentanyl is 13 ml/kg/min and the elimination half-life range is 141–853 minutes. Halothane decreases the clearance of fentanyl by 48%; a similar effect occurs with enflurane. The clearance of fentanyl is decreased in surgical patients with renal impairment and decreased in patients with hepatic impairment. Oral ritonavir (a potent CYP3A4 inhibitor) prolongs the clearance of intravenously administered fentanyl by two-thirds.

Special points

Fentanyl decreases the apparent MAC of co-administered volatile agents and increases the affect of non-depolarizing muscle relaxants to a similar extent as dose halothane. The drug is pharmacologically incompatible with thiopental or methohexital.

It is unknown whether fentanyl is removed by haemodialysis.

The physical and chemical properties of fentanyl make it a suitable agent for transdermal administration. The fentanyl iontophoretic transdermal system works by generating a low-intensity electrical current (activated by the patient) which causes positively charged fentanyl molecules held within a positively charged hydrogel reservoir to be repelled and delivered transdermally into the systemic circulation.

Flecainide

Uses

Flecainide is an antiarrhythmic agent used:

1. for the suppression of irritable foci, e.g. ventricular tachycardia and ventricular ectopics
2. in the treatment of re-entry dysrhythmias, e.g. the Wolff–Parkinson–White syndrome and
3. in the treatment of symptomatic paroxysmal atrial fibrillation intolerant of other medication.

Chemical

An amide type local anaesthetic.

Presentation

As 50/100 mg tablets and as a 10 mg/ml solution of flecainide acetate for intravenous administration.

Main action

A class Ic antiarrhythmic.

Mode of action

Flecainide reduces the maximum rate of depolarization in heart muscle and thereby, slows conduction, particularly in the His–Purkinje system. It has a profound effect on conduction in accessory pathways, especially on retrograde conduction, and markedly suppresses ventricular ectopic foci. It is a local anaesthetic agent which depresses membrane responsiveness and conduction velocity with no effect on the duration of the action potential.

Routes of administration/doses

The adult oral dose is 100–200 mg 12-hourly. Intravenously, flecainide may be administered as a bolus dose of 2 mg/kg over 10 minutes followed by an infusion of 1.5 mg/kg/hour for 1 hour, reducing to 0.25 mg/kg/hour.

Effects

CVS

Flecainide is generally well tolerated; the blood pressure and heart rate usually remain unchanged. The drug has negative inotropic potential.

CNS

Visual disturbances may occur and are probably a central effect of the drug.

Toxicity/side effects

Reversible liver damage, dizziness, paraesthesiae, headaches, and nausea may complicate the use of the drug.

Kinetics

Absorption

Flecainide is rapidly and completely absorbed after oral administration; the bioavailability is 85–90%.

Distribution

Flecainide is 37–58% protein-bound in the plasma; the V_D is 5.8–10 l/kg.

Metabolism

Occurs in the liver to two major metabolites—meta-O-dealkylated flecainide and its lactam.

Excretion

10–50% of the dose is excreted unchanged in the urine. The clearance is 10 ml/min/kg and the elimination half-life is 7–15 hours after intravenous administration and 12–27 hours after oral administration.

Special points

Flecainide increases plasma digoxin levels by 15% when the two drugs are administered concurrently. Hypokalaemia reduces the effectiveness of the drug; a reduced dose should be used in renal or hepatic failure.

Flecainide is not removed by haemodialysis.

Flucloxacillin

Uses

Flucloxacillin is used in the treatment of:

1. respiratory tract infections as an adjunct
2. skin and soft tissue infections
3. osteomyelitis
4. staphylococcal endocarditis and for
5. prophylaxis during surgery.

Chemical

A semi-synthetic isoxazolyl penicillin.

Presentation

As 250/500 mg capsules, in vials containing 250/500/1000 mg of flucloxacillin sodium, and as a syrup containing 25/50 mg/ml of flucloxacillin magnesium.

Main action

Flucloxacillin is an acid-stable, penicillinase-resistant, narrow-spectrum bactericidal antibiotic active against Staphylococcus aureus, group A beta-haemolytic streptococci and pneumococci.

Mode of action

Flucloxacillin acts in the manner typical of penicillins; by binding to a cell wall penicillin-binding protein and thereby interfering with the activity of the enzymes which are involved in the cross-linking of bacterial cell wall peptidoglycans.

Routes of administration/doses

The adult oral and intramuscular dose is 250–500 mg 6-hourly; the corresponding intravenous dose is 250 mg–2 g 6-hourly.

Toxicity/side effects

Gastrointestinal and central nervous system disturbances, rashes, sore throat, and glossitis may complicate the use of the drug. Flucloxacillin may cause both pseudomembranous colitis and jaundice in the critically ill.

Kinetics

Absorption

Flucloxacillin is 50–70% absorbed when administered orally.

Distribution

The drug is 95% protein-bound in the plasma; the V_D is 6.8–9.4 l.

Metabolism

8–13% is metabolized to an active form, 5-hydroxymethyl-flucloxacillin and 4% is hydrolyzed in the liver to penicilloic acid which is inactive.

Excretion

Excretion of the drug occurs by glomerular filtration and tubular secretion, 35–75% of the dose appearing in the urine according to the dose and route of administration. The clearance is 3 ml/min/kg and the elimination half-life is 46 minutes.

Special points

Reduction of the dose of flucloxacillin should be considered if the creatinine clearance is 10 ml/min; the drug is not significantly removed by haemodialysis.

Precipitation occurs if flucloxacillin is co-administered with an aminoglycoside.

Flucloxacillin is not active against MRSA.

Flumazenil

Uses

Flumazenil is used:

1. as an aid to weaning and neurological assessment of ventilated patients who have received benzodiazepine sedation during intensive care
2. as part of the 'wake-up' test during scoliosis surgery
3. to reverse oversedation after endoscopy and
4. for diagnosis of and assessment after benzodiazepine overdose.

Chemical

An imidazobenzodiazepine.

Presentation

As a clear, colourless solution containing 100 micrograms/ml of flumazenil.

Main action

Reversal of the actions of benzodiazepines.

Mode of action

Flumazenil is a competitive antagonist at central benzodiazepine receptors.

Routes of administration/doses

Flumazenil is administered intravenously, titrated in 100 micrograms increments to a total maximum adult dose of 1 mg. It acts in 30–60 seconds and lasts 15–140 minutes. It may also be infused intravenously at 100–400 micrograms/hour.

Toxicity/side effects

Hypertension, dysrhythmias, dizziness, nausea and vomiting, facial flushing, anxiety, and headache have been described. Resedation after prior administration of a benzodiazepine and convulsions in epileptics have also been reported.

Kinetics

Absorption

Flumazenil is well absorbed when administered orally, but undergoes significant first-pass hepatic metabolism.

Distribution

The drug is 50% protein-bound in the plasma; the V_D is 0.9 l/kg.

Metabolism

Flumazenil is extensively metabolized in the liver to a carboxylic acid and glucuronide, both of which are inert.

Excretion

95% is excreted in the urine, 0.1% unchanged. The clearance is 700–1100 ml/min and the elimination half-life is 53 minutes.

Special points

Flumazenil improves the quality of emergence from anaesthesia and reduces post-operative shivering.

Fluoroquinolones

Uses

Fluoroquinolones are used in the treatment of infections of:

1. the respiratory tract
2. skin, soft tissue, bone, and joints
3. ocular, ear, nose, and oral infections
4. gastrointestinal infections
5. genitourinary infections
6. pelvic and intra-abdominal infections
7. gonorrhoea
8. septicaemia and
9. in the prophylaxis/treatment of organisms with the potential for use in bioterrorism.

Chemical

Fluorinated quinolones derived from nalidixic acid.

Presentation

Fluoroquinolones in clinical use include ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin, and all are available for intravenous administration aside from norfloxacin. Ciprofloxacin is available as eye drops and as an eye ointment, as a powder for oral suspension, and in tablet formulations. Ofloxacin is available in an eye drop preparation.

Main action

Fluoroquinolones are bactericidal antibiotics that are active against:

1. Gram-positive bacteria
2. Gram-negative bacteria
3. Gram-positive and negative anaerobes
   There is emerging resistance to fluoroquinolones from a number of species, including *Escherichia coli*, *Shigella*, *Neisseria gonorrhoeae*, *Acinetobacter*, and Pseudomonas spp.

Mode of action

Fluoroquinolones act by inhibiting bacterial DNA gyrase, topoisomerase IV, and type II topoisomerases, thereby inhibiting bacterial DNA replication.

Route of administration/doses

Fluoroquinolones may be administered topically as ointments, orally, or intravenously. The specific dose, route, and frequency of an agent administered are dependent on the clinical indication, age of the patient, and particular agent being used.

Toxicity/side effects

Common side effects include abdominal pain, nausea, and vomiting. Neuropsychiatric disturbances have been reported included anxiety, insomnia, seizures, and hallucinations. Fluoroquinolone use is associated with Achilles tendon rupture, particularly when co-administered with corticosteroids. Allergic reactions, photosensitivity, and transient elevations of liver enzymes have all been reported. The use of these antibiotics is associated with an increased risk of Clostridium difficile and MRSA infection.

Kinetics

Absorption

Fluoroquinolones are generally well absorbed, depending on the specific agent: ciprofloxacin (70–80%), levofloxacin (100%), moxifloxacin (91%). Norfloxacin has a lower bioavailability of 30–40%. Ciprofloxacin undergoes first-pass metabolism. Co-administration of sucralfate or calcium/magnesium/iron salts reduces the amount of drug absorbed.

Distribution

Protein binding of 30–40% is typical of this group of drugs. Norfloxacin has lower protein binding of <15%. The VD for ciprofloxacin is 2–3 l/kg. Fluoroquinolones demonstrate high CSF and tissue penetration.

Metabolism

Fluoroquinolones undergo little hepatic metabolism in man.

Excretion

The majority of fluoroquinolones undergo renal excretion. Ciprofloxacin undergoes active tubular secretion as demonstrated by higher clearance rate of 416–650 ml/min compared to other fluoroquinolones: moxifloxacin (179–246 ml/min) and norfloxacin (275 ml/min). The half-life for these drugs are as follows: ciprofloxacin (3–6.9 hours), levofloxacin (6–8 hours), moxifloxacin (12 hours), norfloxacin (3–4 hours).

Special points

Dose reduction is required in severe renal impairment. 25–30% of an administered dose of ciprofloxacin is removed during haemodialysis.

Ciprofloxacin significantly increases the half-life of co-administered theophylline, necessitating monitoring of plasma concentrations of the latter.

Ciprofloxacin is used in combination therapy in the treatment of *Bacillus anthracus* infection and as a single agent against *Yersinia pestis*. The drug is also used for post-exposure prophylaxis to the following potential bioterrorism organisms: *Bacillus anthracus* (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularaemia).

Antimicrobial agents should always be administered following consideration of local pharmacy and microbiological policies.

Furosemide

Uses

Furosemide is used in the treatment of:

1. oedema of cardiac, renal, or hepatic origin
2. chronic renal insufficiency
3. hypertension
4. raised intracranial pressure
5. symptomatic hypercalcaemia and
6. conversion of oliguric to polyuric renal failure.

Chemical

An anthranilic acid (sulphonamide) derivative.

Presentation

As a clear solution (which must be protected from light) for injection containing 10 mg/ml and as 20/40/500 mg tablets of furosemide. A syrup containing 20/40/50 mg in 5 ml is available. A number of fixed dose combinations with amiloride, triamterene, spironolactone, and potassium chloride are also available.

Main action

Diuresis.

Mode of action

Furosemide acts by inhibition of active chloride ion reabsorption in the proximal tubule and ascending limb of the loop of Henle—by reducing the tonicity of the renal medulla, a hypotonic or isotonic urine is produced. The mechanism of action at a cellular level may be exerted via inhibition of Na^+K^+ATPase or by inhibition of glycolysis.

Routes of administration/doses

The adult oral dose is 20–2000 mg daily, the intramuscular dose is 20–50 mg. Intravenous administration is titrated according to response—a range of 10–1000 mg is recommended. The infusion rate should not exceed 4 mg/min as ototoxicity may result.

Effects

CVS/RS

Pulmonary and systemic vasodilation occur, leading to symptomatic relief of breathlessness prior to diuresis.

GU

A diuresis occurs within a few minutes and lasts 2 hours when furosemide is administered intravenously; correspondingly, diuresis starts 1 hour after oral administration and lasts 4–6 hours. Free water clearance is increased by the drug. The renal blood flow is increased and redistributed in favour of inner corticomedullary flow. Oxygen consumption in the loop of Henle is reduced to basal levels and may protect the kidney from ischaemia.

Metabolic/other

The drug causes a metabolic alkalosis and may be diabetogenic; the serum urate concentrations are increased.

Toxicity/side effects

Hypokalaemia, hypocalcaemia, hypomagnesaemia, and metabolic alkalosis may occur after the administration of furosemide.

Transient auditory nerve damage, pancreatitis, skin rashes, and bone marrow depression have been reported. Furosemide causes interstitial nephritis in high doses; this is a common cause of acute renal failure when co-administered with an aminoglycoside—the two drugs are synergistic in this respect. Deafness is also more likely to result when furosemide and an aminoglycoside are co-administered.

Kinetics

Absorption

Furosemide is 60–70% absorbed after oral administration; the bioavailability by this route is 43–71%.

Distribution

The drug is 96% protein-bound in the plasma, almost exclusively to albumin. The V_D is 0.11–0.13 l/kg.

Metabolism

Furosemide appears to be metabolized primarily in the kidney to a glucuronide.

Excretion

80% is excreted in the urine as unchanged and glucuronidated furosemide, the rest appears in the faeces. The clearance is 2.2 ml/min/kg and the elimination half-life is 45–92 minutes.

Special points

The effects of non-depolarizing muscle relaxants may be enhanced by furosemide, probably due to hypokalaemia. The response to concurrently administered vasopressors may be diminished and that to vasodilators enhanced, both phenomena being manifestations of a contracted circulating blood volume.

The drug is not removed by haemodialysis.







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Gabapentin

Uses

Gabapentin is used in the treatment of:

1. post-herpetic neuralgia
2. painful diabetic neuropathy
3. partial seizures with or without secondary generalization and
4. neuropathic pain.



Chemical

An acetic acid derivative which is a structural analogue of GABA.

Presentation

As 600/800 mg tablets and 100/300/400 mg capsules.



Main actions

Anticonvulsant and analgesic.

Mode of action

Gabapentin is structurally related to GABA, but does not interact with GABA receptors. The binding site for the drug is the alpha-2–delta subunit of voltage-gated calcium channels. Gabapentin does not interact with sodium channels *in vitro* (cf. phenytoin, carbamazepine). It may also:

1. partially reduce the response to the glutamate agonist, NMDA
2. reduce the release of monoamine neurotransmitters *in vitro*
3. stimulate glutamate decarboxylase (the enzyme which converts glutamate to GABA) and
4. increase the synaptic release of GABA.

Route of administration/doses

The drug is administered orally and for all indications, a titration scheme can be employed during initiation of therapy. Alternatively, an initially dose of 300 mg three times daily may be used. Dosage required for long-term epilepsy treatment is determined on an individual basis although clinical trial data demonstrates the effective dosing range to between 900 to 3600 mg/day. Typically, dosage for treatment of neuropathic pain is up to 1800 mg/day although a maximum dose of 3600 mg/day can be used. If discontinuation of gabapentin therapy is to be undertaken, this should be performed gradually over a minimum of 1 week regardless of the indication. The total daily dose of the drug should be reduced in patients with renal impairment.

Effects

CNS

Gabapentin has analgesic and anticonvulsant properties and improves sleep in patients with neuropathic pain.

Toxicity/side effects



Dizziness, ataxia, nystagmus, somnolence, tremor, diplopia, nausea, and vomiting occur with a frequency >5%. Leucopaenia, erectile dysfunction, and weight gain have all been reported following use of the drug.

Kinetics

Absorption

Gabapentin is well absorbed orally and has a bioavailability of 60%. Peak plasma levels of the drug occur within 2–3 hours of administration.

Distribution

The drug is not bound to plasma proteins; the V_D is 0.85 l/kg. In patients with epilepsy, gabapentin concentrations in CSF are approximately 20% of corresponding steady-state trough plasma concentrations. The drug is present in the breast milk of breastfeeding women.

Metabolism

Gabapentin is not metabolized in man and does not induce hepatic mixed function oxidase enzymes.

Excretion

The drug is excreted unchanged by renal excretion. The elimination half-life is 5–7 hours. The clearance is directly proportional to creatinine clearance.

Special points

Gabapentin enhances the analgesic effect of co-administered morphine. It is removed by haemodialysis. The bioavailability of the drug decreases with increasing dose which may minimize toxicity resulting from overdose. Co-administration of gabapentin with antacids containing aluminium and magnesium may reduce bioavailability of the drug by up to 24%.

Gelatins

Uses

Gelatins are used as plasma volume substitutes to expand and maintain circulating blood volume.

Chemical

Animal collagen derivatives. Two types of gelatin are available: succinylated gelatins (molecular weight: 30 000 Da) and urea-linked gelatins (molecular weight: 35 000 Da). They are produced by the thermal degradation of bovine gelatin.

Presentation

A number of agents are available in the UK for intravenous administration. Examples of commercially available products include:

- Gelofusin® 4%, a succinylated gelatin
- Volplex® 4%, a succinylated gelatin
- Haemaccel® 3.5%, a urea-linked gelatin.

The above agents are presented in 0.9% sodium chloride for intravenous administration. Haemaccel® also contains the following electrolytes: K^+ 5.1 mmol/l, Ca^{2+} 6.25 mmol/l.

Main action

Intravascular volume expansion.

Mode of action

Temporary increase in plasma oncotic pressure.

Route of administration/doses

The specific dose of an agent administered is dependent on the clinical indication, the haemodynamic status of the patient, and particular agent being used.

Effects

CVS

The haemodynamic effects of gelatins are proportional to the prevailing circulating volume. The duration of action of these agents depends on the specific agent in use.

Toxicity/side effects

The most important side effect is that of overtransfusion, leading to pulmonary oedema. Administration of gelatins dissolved in saline containing solvents may lead to a hypernatraemic, hyperchloraemic metabolic acidosis. Hyperkalaemia and hypercalcaemia may complicate the use of agents containing solvents that include the electrolytes, potassium and calcium. Allergic reactions have been reported following the use of these agents.

Kinetics

Data are incomplete.

Distribution

Gelatin-containing solutions are initially distributed into the plasma, but later equilibrate with the extracellular fluid compartment following excretion of the gelatin component.

Metabolism

In vitro studies suggest that gelatins are degraded by proteolytic enzymes into smaller peptides and amino acids.

Excretion

Approximately 75% is excreted via the urine. Gelatins have a half-life of approximately 4 hours.

Special points

Following renal excretion, gelatins have an osmotic diuretic effect within the renal tubules. Agents containing calcium should not be administered immediately following a blood transfusion through the same intravenous line without the giving set being flushed with saline. The ionic calcium component may enhance digoxin toxicity if administered concurrently.

Glucagon

Uses

Glucagon is recommended for use:

1. in the treatment of hypoglycaemia and
2. to facilitate radiological investigation of the gastrointestinal tract and has been used in the management of
3. cardiogenic shock
4. renal colic
5. acute diverticulitis and
6. propranolol overdose.

Chemical

A polypeptide hormone extracted from the alpha cells of the pancreatic islets of Langerhans.

Presentation

As vials containing 1/10 mg of lyophilized glucagon hydrochloride with lactose—this is reconstituted in glycerol and water prior to use and in prefilled syringes containing 1 mg glucagon.

Main action

Elevation of blood sugar concentration, positive inotropism and chronotropism, and relaxation of smooth muscle.

Mode of action

Glucagon acts via cell membrane receptors which stimulate adenylate cyclase activity, leading to an increase in the intracellular concentrations of cAMP. The final effects of the hormone are mediated via a cascade of protein kinases.

Routes of administration/doses

Glucagon may be administered intravenously, intramuscularly, or subcutaneously in a dose of 1–5 mg for an adult. The drug may also be infused intravenously (diluted in 5% glucose) at a rate of 1–20 mg/hour. Glucagon acts within 1 minute when administered intravenously and in 8–10 minutes when administered intramuscularly or subcutaneously—the ensuing increase in the blood sugar concentration lasts 10–30 minutes.

Effects

CVS

Glucagon has marked positive inotropic and somewhat less marked positive chronotropic effects and acts synergistically with beta-adrenergic agonist drugs in this respect. The drug does not increase myocardial irritability.

AS

The drug reduces tone throughout the entire gastrointestinal tract, including the common bile duct; gastric and pancreatic secretions are simultaneously inhibited.

GU

Glucagon decreases the ureteric tone and has a small effect in improving the renal blood flow and urine output.

Metabolic/other

Glucagon increases gluconeogenesis, glycogenolysis, lipolysis, proteolysis, and ketogenesis, leading to an increase in the blood sugar concentration. It also stimulates the release of endogenous catecholamines and may cause hypokalaemia secondary to an increase in the rate of insulin secretion.

Toxicity/side effects

The drug is usually well tolerated; nausea and vomiting, hypo- or hyperglycaemia, diarrhoea, and allergic phenomena may complicate the use of glucagon.

Kinetics

Absorption

Glucagon is inactive when administered orally. The bioavailability appears to be similar when administered intramuscularly or subcutaneously.

Metabolism

The drug is degraded by proteolysis in approximately equal quantities by splanchnic, hepatic, and renal routes. The precise metabolic pathways are unknown.

Excretion

The clearance is 8–12 ml/min/kg and the elimination half-life is 3–6 minutes.

Special points

The clearance of glucagon is halved in patients with renal failure; the drug is not removed by haemodialysis.

Glucagon potentiates the anticoagulant effect of warfarin, but not that of heparin.

Glucose

Uses

Glucose solutions are used:

1. to provide a source of water (5% solutions) and
2. calories (10/20/50% solutions) and
3. in the treatment of hypoglycaemia.

Chemical

Glucose is D-glucopyranose D-glucose monohydrate, a monosaccharide obtained by the hydrolysis of cornstarch.

Presentation

As a clear, colourless sterile solution containing 5/10/20/50% glucose in water in ampoules or bags containing 500/1000 ml. The preparations are sterile and contain no buffers or bacteriostatic agents. The pH varies from 3.5–6.5, according to concentration. The 5% solution contains 170 kCal/l and has an osmolarity of 250 mOsm/l; the 10/20/50% solutions are appropriate multiples of these figures.

Main action

An increase in the blood sugar concentration and glycogen deposition; ketosis and nitrogen loss are decreased.

Route of administration/doses

Glucose solutions are administered intravenously; the 20% and 50% solutions should preferably be administered via a central vein. The dose depends upon the state of hydration, nutritional requirements, and blood sugar concentration of the individual patient.

Effects

CVS

The haemodynamic effects of glucose solutions are proportional to the prevailing volaemic status; infusion of the crystalloid will temporarily restore cardiovascular parameters towards normal.

GU

Renal perfusion is temporarily restored towards normal in hypovolaemic subjects transfused with the crystalloid.

Toxicity/side effects

Overhydration leading to water intoxication, hyponatraemia, mental confusion, and fits may occur with injudicious use of isotonic solutions (5%). This may produce central pontine myelinolysis. Hyperglycaemia and venous thrombosis may occur with the 10/20/50% solutions.

Kinetics

Data are incomplete.

Absorption

Glucose is rapidly and completely absorbed when administered orally.

Distribution

Glucose solutions are initially distributed within the intravascular compartment and rapidly equilibrate within the intra- and extravascular space.

Metabolism

Glucose is completely metabolized to carbon dioxide and water.

Excretion

The metabolic products are excreted via the lungs and kidneys.

Special points

Use of excessive quantities of glucose solutions (especially in premenopausal women and prepubertal children) may result in cerebral oedema and respiratory arrest, a condition associated with poor neurological outcome.

Glyceryl trinitrate

Uses

Glyceryl trinitrate is used in the treatment of:

1. stable, unstable, and variant angina
2. left ventricular failure secondary to myocardial infarction and
3. in the perioperative control of blood pressure and
4. for the prophylaxis of phlebitis associated with venous cannulation and may be of use in
5. decreasing infarct size in patients with acute myocardial infarction and used
6. to promote venodilation when administering peripheral total parenteral nutrition.

Chemical

An organic nitrate which is an ester of nitric acid.

Presentation

As 300/500/600 micrograms tablets for sublingual administration, 1/2/3/5 mg tablets for buccal administration, an oral spray delivering 400 micrograms per metered dose, a slow-release transdermal patch delivering 5/10 mg per 24 hours, and as a clear solution for injection (which must be protected from light) containing 0.5/1/5 mg/ml of glyceryl trinitrate.

Main action

Vasodilation of both arteries and veins.

Mode of action

Glyceryl trinitrate acts on the enzyme, nitric oxide, stimulating guanylate cyclase in the vascular smooth muscle cells, resulting in the relaxation of smooth muscles.

Routes of administration/doses

The adult dose is 0.3 mg by the sublingual route, 0.4–0.8 mg when delivered by buccal spray, 1–5 mg when delivered by the buccal route in tablet form, 5–10 mg/24 hours when administered transdermally, and (diluted in glucose or saline) at the rate of 10–400 micrograms/min when administered intravenously. The maximum effect occurs in 15–30 minutes when administered buccally or sublingually and 90–120 seconds after intravenous administration.

Effects

CVS

At low dose ranges, glyceryl trinitrate causes venodilation and at higher concentrations, venous and arterial vasodilation. The systolic blood pressure decreases more than does the diastolic blood pressure; the central venous pressure, pulmonary artery pressure, left ventricular end-diastolic pressure, and myocardial oxygen consumption all decrease with the use of glyceryl trinitrate. The cardiac output is usually unaltered or decreased slightly by administration of the drug; it may increase in patients with heart failure who have a high systemic vascular resistance. The coronary blood flow may decrease or remain unchanged. A reflex tachycardia occurs in normal subjects; no effect is observed on the heart rate in patients with heart failure. Glyceryl trinitrate reduces venous return (preload) and facilitates subendocardial blood flow with redistribution into ischaemic areas. It relieves coronary vasospasm and dilates arterioles reducing afterload and is thought to relieve angina primarily by reducing myocardial oxygen demand (secondarily to a fall in left ventricular end-diastolic pressure and myocardial wall tension); myocardial oxygen supply is simultaneously increased by redistribution of the coronary blood flow to the subendocardium.

RS

The drug causes bronchodilatation; intrapulmonary shunting may increase, but the mechanism of hypoxic pulmonary vasoconstriction appears to be unaffected in man.

CNS

The intracranial pressure may increase due to cerebral vasodilation.

AS

Glyceryl trinitrate relaxes the smooth muscle of the gastrointestinal and biliary tracts.

GU

The renal blood flow may decrease in patients with congestive cardiac failure secondary to a fall in blood pressure with no accompanying change in renal vascular resistance.

Toxicity/side effects

Hypotension, sinus tachycardia and, occasionally, bradycardia, nausea, and vomiting may result from administration of the drug. Headaches occur more commonly with oral or sublingual than with intravenous administration.

Kinetics

The data vary widely.

Absorption

Absorption is rapid and efficient after sublingual administration, but slow after oral or transdermal administration; the bioavailability is 3% after oral administration due to a significant first-pass effect.

Distribution

Glyceryl trinitrate is 60% protein-bound in the plasma in animal models; the V_D is 0.04–2.9 l/kg.

Metabolism

The drug is rapidly metabolized in the liver and red blood cells by reduction to dinitrates, mononitrates, and nitrites, all of which are less active than the parent compound.

Excretion

80% is excreted in the urine; trace amounts are exhaled as carbon dioxide. The clearance after intravenous administration is 0.3–1 l/min/kg and the elimination half-life is 1–3 minutes.

Special points

40–80% of the dose of intravenous glyceryl trinitrate is adsorbed onto plastic giving sets. The drug has been shown to increase the duration of pancuronium-induced neuromuscular blockade and may also slow the catabolism of opioids. Clinically important tolerance does not occur with continued intravenous administration of the drug.

The drug is not removed by dialysis.

Excess cardiovascular mortality has been noticed with the use of nitrates and sildenafil.

Glycopyrronium bromide

Uses

Glycopyrronium bromide is used:

1. in premedication where an antisialogogue action is desired
2. to protect against the peripheral muscarinic effects of anticholinesterases
3. for the treatment of bradycardias in anaesthetized patients
4. for the treatment of hyperhydrosis (via topical administration) and
5. for symptom control in palliative care.

Chemical

A quaternary ammonium compound.

Presentation

As a clear solution for injection containing 0.2 mg/ml of glycopyrronium bromide and as a powder for topical application. It is also supplied in a fixed dose combination containing 0.5 mg of glycopyrronium bromide and 2.5 mg of neostigmine per ml.

Main action

Anticholinergic; glycopyrronium bromide has a particularly profound anti-secretory action.

Mode of action

Glycopyrronium bromide acts by competitive antagonism of acetylcholine at peripheral muscarinic receptors.

Routes of administration/doses

The adult intravenous and intramuscular dose is 0.2–0.4 mg; the paediatric dose is 4–10 micrograms/kg. The peak effect occurs 3 minutes after intravenous injection.

Effects

CVS

Glycopyrronium bromide has little effect on the blood pressure when used in normal doses and causes less dysrhythmias than atropine. Tachycardia occurs when the drug is administered intravenously in doses greater than 0.2 mg to anaesthetized patients. Glycopyrronium bromide is protective against bradycardias due to the oculocardiac reflex or suxamethonium when administered intravenously. The vagolytic effects of the drug last approximately 2–3 hours.

RS

The drug has a significant and long-lasting bronchodilator effect and causes an increase in the physiological dead space.

CNS

Glycopyrronium bromide is unable to cross the blood–brain barrier and is theoretically devoid of any central effects; however, headache and drowsiness are well recognized sequelae of the drug. Post-anaesthetic recovery appears to be significantly more rapid with glycopyrronium bromide than with atropine. Glycopyrronium bromide has no effect on pupil size or accommodation.

AS

The drug has a powerful antisialogogue effect that lasts approximately 8 hours after intravenous or intramuscular injection—the drug is five times as potent as atropine in this respect. Glycopyrronium bromide reduces gastric volume by 90% for 4 hours after administration and reduces antral motility. The drug reduces lower oesophageal sphincter tone.

Metabolic/other

The drug inhibits sweat gland activity, but little effect is produced on body temperature. Glycopyrronium bromide has a weak local anaesthetic action.

Toxicity/side effects

Typical anticholinergic side effects are produced by the drug; dry mouth, difficulty in micturition, and inhibition of sweating.

Kinetics

Absorption

Oral absorption is poor and erratic; bioavailability by this route is 5%. The drug seems to be absorbed in comparable amounts when administered by either the intramuscular or intravenous route.

Distribution

Redistribution of the drug occurs rapidly—90% disappears from the plasma in 5 minutes. The drug crosses the placenta and may cause a fetal tachycardia. The V_D is 0.2–0.64 l/kg.

Metabolism

In animals, glycopyrronium bromide occurs by hydroxylation and oxidation in the liver; very little biotransformation of the drug occurs in man.

Excretion

Excretion occurs in the urine (85%) and bile (15%), and 80% unchanged. The clearance of glycopyrronium bromide is 0.89 l/min and the elimination half-life is 0.6–1.1 hours.

Special points

When used in combination with neostigmine to reverse non-depolarizing neuromuscular blockade, glycopyrronium bromide causes less initial tachycardia and less anticholinesterase-induced late bradycardia than atropine (and control of secretions is superior) due to the fact that the time course of action of neostigmine and glycopyrronium bromide are better matched.

The drug is physically incompatible with thiopental, methohexital, and diazepam.







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Haloperidol

Uses

Haloperidol is used in the treatment of:

1. schizophrenia and related psychoses
2. nausea and vomiting
3. motor tics and hiccupping
4. acute confusional states and delirium in critical care
5. for premedication and
6. palliative care.

Chemical

A butyrophenone derivative.

Presentation

As 0.5/1.5/5/10/20 mg tablets, a syrup containing 2/10 mg/ml, and as a clear solution for injection containing 5 mg/ml of haloperidol. A depot preparation containing 50/100 mg/ml of haloperidol decanoate is also available.

Main action

Antiemetic and neuroleptic.

Mode of action

The antiemetic and neuroleptic effects of the drug appear to be mediated by:

1. central dopaminergic (D2) blockade, leading to an increased threshold for vomiting at the chemoreceptor trigger zone and
2. post-synaptic GABA antagonism.

Routes of administration/doses

The adult oral dose is 1–15 mg daily in divided doses. The initial intramuscular dose is 2–30 mg, with additional doses of 5 mg until the symptoms are controlled. The intravenous dose is 1–5 mg. The drug has a longer duration of action than droperidol.

Effects

CVS

Haloperidol has minimal cardiovascular effects, but its antagonistic effects at alpha-adrenergic receptors may lead to hypotension in the presence of hypovolaemia.

RS

The drug has minimal effect on respiration.

CNS

Haloperidol induces neurolepsis; a state characterized by diminished motor activity, anxiolysis, and indifference to the external environment. The seizure threshold is raised by the drug.

AS

The drug has a powerful antiemetic effect via a central effect at the chemosensitive trigger zone.

Metabolic/other

Haloperidol, in common with other dopamine antagonists, may cause hyperprolactinaemia.

Toxicity/side effects

Extrapyramidal effects occur relatively commonly during the use of haloperidol; these include the neuroleptic malignant syndrome (a complex of symptoms that include catatonia, cardiovascular lability, hyperthermia, and myoglobinaemia) which has a mortality in excess of 10%. Gastrointestinal and haemopoietic disturbances, abnormalities of liver function tests, and allergic phenomena have been reported after the use of the drug.

Kinetics

Absorption

The drug is well absorbed after oral administration; the bioavailability by this route is 50–88%.

Distribution

The drug is 92% protein-bound in the plasma; the V_D is 18–30 l/kg.

Metabolism

Haloperidol is extensively metabolized in the liver; a reduced metabolite may be active.

Excretion

The clearance is 11.3 ml/min/kg and the elimination half-life is 10–38 hours, dependent upon the route of administration.

Special points

Haloperidol is the preferred agent for the treatment of delirium in the critically ill adult. The sedative effects of the drug are additive with those of other central nervous system depressants administered concurrently. Hypotension resulting from the administration of the drug should not be treated using adrenaline as a further decrease in the blood pressure may result.

Haloperidol is not removed by dialysis.

Halothane

Uses

Halothane is used for the induction and maintenance of general anaesthesia.

Chemical

A halogenated hydrocarbon containing bromine, chlorine, and fluorine.

Presentation

As a clear, colourless liquid (that should be protected from light) with a characteristic sweet smell. The commercial preparation contains 0.01% thymol which prevents decomposition on exposure to light; it is non-flammable in normal anaesthetic concentrations. The molecular weight of halothane is 197.4, the boiling point 50.2°C, and the saturated vapour pressure is 32 kPa at 20°C. The MAC of halothane is 0.75 (0.29 in the presence of 70% nitrous oxide), the oil/water solubility coefficient 220, and the blood/gas solubility coefficient 2.5. The drug is readily soluble in rubber; it does not attack metals in the absence of water vapour, but will attack brass, aluminium, and lead in the presence of water vapour.

Main actions

General anaesthesia (reversible loss of both awareness and recall of noxious stimuli).

Mode of action

The mechanism of general anaesthesia remains to be fully elucidated. General anaesthetics appear to disrupt synaptic transmission (especially in the area of the ventrobasal thalamus). The mechanism may include potentiation of GABA and glycine receptors and antagonism at NMDA receptors. Their mode of action at the molecular level appears to involve expansion of hydrophobic regions in the neuronal membrane, either within the lipid phase or within hydrophobic sites in cell membrane proteins.

Routes of administration/doses

Halothane is administered by inhalation, conventionally via a calibrated vaporizer. The concentration used for the inhalational induction of anaesthesia is 2–4% and for maintenance 0.5–2%.

Effects

CVS

Halothane causes a dose-related decrease in myocardial contractility and cardiac output, with an attendant decrease in cardiac work and myocardial oxygen consumption, possibly by inhibition of calcium ion flux within myocardial cells and of the interaction between calcium ions and the contractile proteins. The heart rate decreases as a result of vagal stimulation; the systemic vascular resistance is decreased by 15–18%, leading to a decrease in systolic and diastolic blood pressure; halothane also obtunds the baroreceptor reflexes. The drug has little effect on coronary vascular resistance. The threshold potential and refractory period of myocardial cells are increased; the drug also decreases the rate of phase IV repolarization. Halothane causes marked sensitization of the myocardium to catecholamines, although it does not itself increase the concentration of circulating catecholamines.

RS

Halothane is a respiratory depressant, markedly decreasing the tidal volume, although the respiratory rate may increase. A slight increase in $PaCO_2$ may result in spontaneously breathing subjects; the drug also decreases the ventilatory response to hypoxia and hypercapnia and inhibits the mechanism of hypoxic pulmonary vasoconstriction. Halothane is non-irritant to the respiratory tract; it causes bronchodilatation by a direct effect on the bronchial smooth muscle and also inhibits histamine-induced bronchoconstriction. Bronchial secretions are reduced by the drug.

CNS

The principal effect of halothane is general anaesthesia; the drug has little, if any, analgesic effect. The drug causes cerebral vasodilation, leading to an increase in both the cerebral blood flow and intracranial pressure; it also decreases cerebral oxygen consumption. A centrally mediated decrease in skeletal muscle tone results from the use of halothane.

AS

The drug decreases salivation and gastric motility; splanchnic blood flow decreases as a result of the hypotension the drug produces.

GU

Halothane decreases renal blood flow by 40% and the glomerular filtration rate by 50%; a small volume of concentrated urine results. The drug reduces the tone of the pregnant uterus.

Metabolic/other

Halothane decrease plasma noradrenaline concentration whilst increasing the concentrations of levothyroxine and growth hormone. It also inhibits leucocyte phagocytosis. The drug causes a fall in body temperature, predominantly by cutaneous vasodilation. Halothane causes a significant decrease in nitric oxide synthase activity.

Toxicity/side effects

Halothane is a potent trigger agent for the development of malignant hyperthermia. The drug may also cause the appearance of myocardial dysrhythmias, particularly in the presence of hypoxia, hypercapnia, or excessive catecholamine concentrations. Shivering ('halothane shakes') may occur post-operatively. The most serious side effect, halothane hepatitis, occurs (rarely) after the repeated use of the drug in the same individual. Halothane hepatitis is thought to be the result of an immune reaction to a metabolite formed by a reductive metabolic pathway. The risk of this complication is increased by obesity, perioperative hypoxaemia, and a short interval between consecutive exposures. It has been recommended that a period of at least 6 months should elapse prior to repeated administration of the drug to any individual.

Kinetics

Absorption

The major factors affecting the uptake of volatile anaesthetic agents are solubility, cardiac output, and the concentration gradient between the alveoli and venous blood. Halothane is relatively insoluble in blood; alveolar concentration, therefore, reaches inspired concentration relatively rapidly, resulting in a rapid induction of anaesthesia. An increase in the cardiac output increases the rate of alveolar uptake and slows the induction of anaesthesia. The concentration gradient between alveoli and venous blood approaches zero at equilibrium; a large concentration gradient favours the onset of anaesthesia.

Distribution

The drug is initially distributed to organs with a high blood flow (the brain, heart, liver, and kidney) and later to less well-perfused organs (muscles, fat, and bone).

Metabolism

20% of an administered dose is metabolized in the liver via cytochrome P450 2EI, principally by oxidation and dehalogenation to yield trifluoroacetic acid, trifluoroacetylethanolamide, chlorobromodifluorethylene, and chloride and bromide radicals.

Excretion

60–80% is exhaled unchanged; the metabolites are excreted in the urine. Excretion of metabolites may continue for up to 3 weeks after the administration of halothane.

Special points

Halothane potentiates the action of co-administered non-depolarizing relaxants. The dose of co-administered adrenaline should not exceed 10 ml of a 1:100 000 solution in a 10-minute period to guard against the development of ventricular dysrhythmias.

Hartmann's solution

Uses

Hartmann's solution is used:

1. in the treatment of dehydration
2. for the acute expansion of intravascular volume and
3. to provide maintenance fluid and electrolyte requirements in the perioperative period.

Chemical

Compound sodium lactate.

Presentation

As a clear, colourless sterile solution in 500/1000 ml bags containing 131 mmol of sodium ions, 111 mmol of chloride ions, 2 mmol of calcium ions, 5 mmol of potassium ions, and 29 mmol of lactate ions (which are converted to bicarbonate ions in the liver) per litre. The pH of the solution is 6–7.3.

Main action

Intravascular volume expansion.

Routes of administration/doses

Hartmann's solution is administered intravenously at a rate titrated against the patient's clinical status.

Effects

CVS

The haemodynamic effects of Hartmann's solution are proportional to the prevailing circulating volume and are short-lived.

GU

Renal perfusion is temporarily restored towards normal in hypovolaemic patients transfused with the crystalloid.

Metabolic/other

1 litre of one-sixth molar sodium lactate is potentially equivalent to 290 ml of 5% sodium bicarbonate in its acid-neutralizing effect and to 600 ml of 5% glucose in its antiketogenic effect.

Toxicity/side effects

The predominant hazard is that of overtransfusion, leading to hypernatraemia, pulmonary oedema, and metabolic alkalosis.

Kinetics

Data are incomplete.

Distribution

Hartmann's solution is initially distributed into the plasma, but later equilibrates with the extracellular fluid.

Metabolism

The lactate component is oxidized in the liver to bicarbonate and glycogen over a period of about 2 hours. This is dependent on cellular oxidative activity and the mechanism may be depressed by hypoxia and liver dysfunction.

Excretion

Via the urine.

Heparin

Uses

Heparin is used for:

1. the prevention of venous thromboembolic disease
2. the priming of haemodialysis and cardiopulmonary bypass machines and for maintaining the patency of indwelling lines and the treatment of
3. disseminated intravascular coagulation
4. fat embolism and
5. in the treatment of acute coronary syndromes.

Chemical

Commercial heparin is a mixture of acid mucopolysaccharides (of molecular weight 3000–60 000 Da) extracted from bovine lung or porcine intestinal mucosa.

Presentation

Low-molecular weight heparins (LMWH) are also available. These agents consist of short polysaccharide chains which have an average molecular weight of less than 8000 Da.

Main action

Anticoagulant.

Mode of action

The drug acts by binding reversibly to antithrombin III and enhancing its ability to inhibit certain proteases in the coagulation cascade (XIII, XII, XI, X, IX, plasmin, and thrombin). It also binds directly to several coagulation proteases and thereby facilitates their reaction with antithrombin III. LMWH acts via antithrombin III to inhibit factor Xa.

Route of administration/doses

The intravenous dose of heparin is titrated (at approximately 1000 IU/hour) to maintain activated partial thromboplastin time at 1.5–2 times the control value. The subcutaneous dose is 5000 IU 8–12-hourly. 1 IU of heparin will prevent 1 ml of citrated sheep plasma from clotting for 1 hour after the addition of 0.2 ml of 1:100 calcium chloride solution. Heparin sodium contains at least 120 IU/mg. LMWHs are available for subcutaneous and intravenous use. The dose and route of LMWH administration is dependent on the clinical indication and specific agent being used.

Effects

Metabolic/other

In addition to its anticoagulant effects, heparin inhibits platelet aggregation by fibrin. Heparin increases hepatic triglyceride and other lipase activities in plasma, leading to an increase in plasma free fatty acid concentration.

Toxicity/side effects

Excessive bleeding is the most commonly reported side effect; osteoporosis and aldosterone suppression have also been reported. Thrombocytopaenia occurs in approximately 5% of patients who receive the drug and occurs more commonly when bovine heparin is used. This may be asymptomatic or be associated with life-threatening arterial and venous thromboses, a condition which carries a mortality of 30%.

Kinetics

Absorption

There are no data concerning oral administration. The bioavailability appears to be the same for intravenous and subcutaneous administration.

Distribution

One-third is bound in the plasma to antithrombin III and the rest to albumin, fibrinogen, and proteases. The V_D is 40–100 ml/kg.

Metabolism

Heparin appears to be desulphated and depolymerized (by heparinases) in the liver, kidneys, and reticulo-endothelial system.

Excretion

Small amounts are excreted unchanged in the urine; renal impairment has little effect on the pharmacokinetics of heparin. The clearance is 0.5–2 ml/kg/min and the elimination half-life is 0.5–2.5 hours. Heparin elimination is markedly decreased during hypothermia, e.g. during cardiopulmonary bypass.

Special points

During heparin therapy, the thrombin time, whole blood clotting time, and activated partial thromboplastin time (kaolin cephalin time) are all prolonged. The bleeding time is unaffected by heparin and the drug has no fibrinolytic activity. Specific antagonism of the effects of heparin may be achieved by the use of protamine (q.v.).

Neuroaxial anaesthesia and heparin therapy requires careful consideration. Data suggests that at least 4 hours should elapse from the discontinuation

of an unfractionated heparin infusion to initiation of neuroaxial anaesthesia. If a patient has received LMWH for thromboembolism prophylaxis, then at least 12 hours should elapse prior to spinal/epidural insertion. If a treatment dose has been administered, then neuroaxial anaesthesia should be delayed by 24 hours.

LMWHs may be partially reversed using protamine (maximum effect <60%). Limited data suggest that in the first 8 hours following administration of LMWH, 1 mg of protamine 'reverses' 1 mg of LMWH up to maximum dose of protamine that can be safely given. The effect of LMWH decreases over time with a 50% reduction in effect by approximately

8 hours and <33% effect after 12 hours.

LMWH has the apparent advantages of once-daily administration, safety during pregnancy, and causing thrombocytopaenia less frequently.

Heparin is not removed by haemodialysis.

Human albumin solution (HAS)

Uses

HAS is used:

1. for plasma volume replacement in haemorrhage, burns, or excessive fluid and electrolyte loss
2. for the priming of extracorporeal circuits
3. in the treatment of hypoalbuminaemic states and
4. as a replacement fluid during therapeutic plasma exchange.

Chemical

A protein solution.

Presentation

As a clear, straw-coloured fluid for infusion containing 4.5/5/20/25% of protein (of which 96% is albumin); the solutions contain sodium carbonate, sodium bicarbonate and/or acetic acid to adjust the pH to 6.4–7.4 and stabilizers, but no preservatives. The solutions are prepared from pooled venous plasma from healthy subjects who are HepBsAg and HIV negative; the solutions are pasteurized at 60°C for 10 hours. The sodium content of HAS is 130–160 mmol/l.

Main actions

Plasma volume expansion and reversal of hypoalbuminaemia.



Mode of action

Albumin is intimately involved in the regulation of plasma volume due to its colloid oncotic pressure; 5% HAS is iso-oncotic, but 20/25% HAS will draw 3/3.5 times the administered volume into the circulation from the tissues within 15 minutes.

Routes of administration/doses

HAS is administered by intravenous infusion according to clinical requirements; the haematocrit should be monitored and maintained above 25%—circulatory overload must be avoided.

Effects

CVS

The haemodynamic effects of HAS are proportional to the prevailing volaemic status; in the face of hypovolaemia, HAS infusion restores cardiovascular parameters towards normal. Myocardial depression has been reported with HAS. Although it contains no clotting factors, HAS does not interfere with the mechanism of blood clotting.

GU

Renal perfusion is restored towards normal in hypovolaemic subjects transfused with the colloid.

Toxicity/side effects

The major concern with the use of HAS is circulatory overload. Allergic reactions and aluminium toxicity occur infrequently.

Kinetics

Data are incomplete.

Metabolism

Exogenous albumin enters the amino acid pool and undergoes biotransformation within the liver.

Excretion

The elimination half-life is 16–18 days.

Special points

HAS does not inhibit endothelial activation in sepsis. There is little evidence to support the use of albumin to improve outcome in the critically ill. Its effects on plasma volume are not predictable, especially in pathological states associated with leaky capillary membranes.

Hydralazine

Uses

Hydralazine is used in the treatment of:

1. chronic moderate to severe hypertension
2. acute, severe hypertension
3. pre-eclampsia and
4. congestive heart failure.

Chemical

A phthalazine derivative.

Presentation

As 25/50 mg tablets of hydralazine hydrochloride, in ampoules containing 20 mg of hydralazine hydrochloride, as a white lyophilized powder which is reconstituted prior to use in water.

Main action

Peripheral vasodilation.

Mode of action

Hydralazine appears to act directly on vascular smooth muscle by interfering either with calcium entry into the cell or the release of calcium from intracellular stores; this leads to electromechanical decoupling and inhibition of contraction.

Routes of administration/doses

The adult oral dose is 50–200 mg/day in divided doses; the intravenous dose is 20–40 mg administered slowly. The drug takes 15–20 minutes to act when administered intravenously and has a duration of action of 2–6 hours.

Effects

CVS

Hydralazine causes predominantly arteriolar vasodilation, leading to a decrease in the systemic vascular resistance; a compensatory tachycardia develops and the cardiac output increases.

CNS

Cerebral blood flow increases after the administration of hydralazine.

GU

The renal blood flow increases secondarily to the increased cardiac output; however, hydralazine usually produces sodium retention and a decrease in urine volume.

Metabolic/other

Plasma renin activity is increased by the drug.

Toxicity/side effects

Minor side effects such as headache, flushing, sweating, nausea, and vomiting are common. The drug may precipitate angina in patients with myocardial ischaemia. A lupus-like syndrome may occur when high doses are used. Peripheral neuropathies and blood dyscrasias occur rarely with the use of hydralazine.

Kinetics

Absorption

The bioavailability of oral hydralazine is dependent on the acetylator status and thus the extent of first-pass metabolism; average values are 16–35%.

Distribution

Hydralazine is 87% protein-bound in the plasma; the V_D is 4.2 l/kg.

Metabolism

The drug is primarily metabolized by acetylation and oxidation with subsequent conjugation. Phenotypically determined populations of fast and slow acetylators exist.

Excretion

50–90% is excreted in the urine, 1–2% unchanged. Up to 10% may appear in the faeces. The clearance is 1.4 l/kg/hour and the elimination half-life is 0.67–3.6 hours.

Special points

The drug is commonly used in combination with a beta-adrenergic antagonist to obtund the compensatory tachycardia and increased plasma renin activity caused by hydralazine.

The hypotensive effects of volatile agents and hydralazine are additive. A dose of 0.4 mg/kg has been recommended 10 minutes prior to induction in order to obtund the pressor response to intubation.

The drug crosses the placenta and may produce a fetal tachycardia when used in pregnancy or labour.

The addition of hydralazine to glucose solutions is not recommended.

Hydralazine is not removed by haemodialysis.

Hydrocortisone

Uses

Hydrocortisone is used:

1. as replacement therapy in adrenocortical deficiency states and in the treatment of
2. allergy and anaphylaxis
3. asthma
4. a panoply of autoimmune disorders
5. eczema and contact sensitivity syndromes and
6. in leukaemia chemotherapy regimes and
7. for immunosuppression after organ transplantation.

Chemical

A glucocorticosteroid.

Presentation

As 10/20 mg tablets of hydrocortisone, in vials containing a white lyophilized powder which is diluted in water to yield a solution containing 100 mg of hydrocortisone sodium succinate, and as a variety of topical creams and retention enemas, some of which are fixed dose combinations.

Main action

Anti-inflammatory.

Mode of action

Corticosteroids act by controlling the rate of protein synthesis; they react with cytoplasmic receptors to form a complex which directly influences the rate of RNA transcription. This directs the synthesis of lipocortins.

Routes of administration/doses

The adult dose by the intravenous route is 100–500 mg 6–8-hourly; the drug acts within 2–4 hours and has duration of action of 8 hours when administered intravenously. The corresponding oral dose is 10–20 mg/day, using the lowest dose that is effective and on alternate days, if possible, to limit the development of side effects. The intra-articular dose is 5–50 mg daily.

Effects

CVS

In the absence of corticosteroids, vascular permeability increases, small blood vessels demonstrate an inadequate motor response, and cardiac output decreases. Steroids have a positive effect on myocardial contractility and cause vasoconstriction by increasing the number of alpha-1 adrenoreceptors and beta-adrenoreceptors and stimulating their function.

CNS

Corticosteroids increase the excitability of the central nervous system; the absence of glucocorticoids leads to apathy, depression, and irritability.

AS

Hydrocortisone increases the likelihood of peptic ulcer disease; it also decreases the gastrointestinal absorption of calcium.

GU

Hydrocortisone has weak mineralocorticoid effects and produces sodium retention and increased potassium excretion; the urinary excretion of calcium is also increased by the drug. The drug increases the glomerular filtration rate and stimulates tubular secretory activity.

Metabolic/other

Hydrocortisone exerts profound effects on carbohydrate, protein, and lipid metabolism. Glucocorticoids stimulate gluconeogenesis and inhibit the peripheral utilization of glucose; they cause a redistribution of body fat, enhance lipolysis, and also reduce the conversion of amino acids to protein. Hydrocortisone is a potent anti-inflammatory agent which inhibits all stages of the inflammatory process by inhibiting neutrophil and macrophage recruitment, blocking the effect of lymphokines, and inhibiting the formation of plasminogen activator. Corticosteroids increase red blood cell, neutrophil, and haemoglobin concentrations whilst depressing other white cell lines and the activity of lymphoid tissue.

Toxicity/side effects

Consist of an acute withdrawal syndrome and a syndrome (Cushing's) produced by prolonged use of excessive quantities of the drug. Cushing's syndrome is characterized by growth arrest, a characteristic appearance consisting of central obesity, a moon face and buffalo hump, striae, acne, hirsutism, skin and capillary fragility together with the following metabolic derangements: altered glucose tolerance, fluid retention, a hypokalaemic alkalosis, and osteoporosis. A proximal myopathy, cataracts, and an increased susceptibility to peptic ulcer disease may also complicate the use of the drug.

Kinetics

Absorption

Hydrocortisone is well absorbed when administered orally or rectally; the oral bioavailability is 54% and the rectal bioavailability is 30–90%.

Distribution

The drug is reversibly bound in the plasma to albumin (20%) and a specific corticosteroid-binding globulin (70%); the drug is 90% protein-bound at low concentrations, but only 60–70% protein-bound at higher concentrations. The V_D is 0.3–0.5 l/kg according to the dose.

Metabolism

Occurs in the liver to tetrahydrocortisone.

Excretion

The clearance of hydrocortisone is dose-dependent and ranges from 167–283 ml/min; the elimination half-life is 1.2–1.8 hours.

Special points

Cortisone and hydrocortisone (cortisol) are metabolically interconvertible; only the latter is active. The conversion of cortisone to hydrocortisone is rapid and extensive and occurs as a first-pass effect in the liver. Hydrocortisone is one-quarter as potent as an anti-inflammatory agent as prednisolone. It has been recommended that perioperative steroid cover be given:

1. to patients who have received high-dose steroid replacement therapy for 2 weeks in the preceding year prior to surgery
2. to patients undergoing pituitary or adrenal surgery. Glucocorticoids antagonize the effects of anticholinesterase drugs.

Relative adrenal insufficiency is reported in the critically ill, and low-dose hydrocortisone and mineralocorticoid replacement have been shown to decrease the time to 'shock' reversal and may decrease mortality.

Hyoscine

Uses

Hyoscine is used:

1. in premedication
2. in the prophylaxis of motion sickness
3. as an antispasmodic and
4. in palliative care.



Chemical

Hyoscine is an alkaloid derived from *Scopolia carniolica* and is an ester of tropic acid and scopine. Scopolamine is l-hyoscine.

Presentation

Hyoscine hydrobromide is presented as a clear solution for injection containing 0.4 mg/ml and as a fixed dose combination with papaveretum. Hyoscine butylbromide is presented as a clear solution containing 20 mg/ml and in 10 mg tablet form. A transdermal preparation delivering 1 mg/72 hours of hyoscine is also available.

Main actions

Anticholinergic with marked sedative effects.

Mode of action

The drug acts by competitive antagonism of acetylcholine at muscarinic receptors (hyoscine has little effect at nicotinic receptors).

Routes of administration/doses

Hyoscine may be administered intramuscularly, intravenously, subcutaneously, transdermally, or orally. The intramuscular dose for premedication is 8–15 micrograms/kg. The adult oral dose is 20 mg 6-hourly.

Effects

CVS

Hyoscine has less effect than atropine on cardiovascular parameters. When administered intravenously, an initial tachycardia may be followed by a bradycardia.

RS

The drug causes a marked decrease in bronchial secretions, mild bronchodilatation, and mild stimulation of respiration.

CNS

Hyoscine is a central nervous system depressant, causing 'twilight sleep' and amnesia. It has antanalgesic, antiemetic, and anti-Parkinsonian properties. Hyoscine may also cause the central anticholinergic syndrome.

AS

A marked antisialogogue, hyoscine is also antispasmodic throughout the gut and biliary tree.

GU

The tone of the bladder and ureters is reduced following administration of the drug.

Metabolic/other

Hyoscine has a more marked effect on the eye and sweat gland activity than atropine.

Toxicity/side effects

The central anticholinergic syndrome is the main side effect and may be prolonged, especially in the elderly; peripheral anticholinergic side effects may also occur following the use of hyoscine.

Kinetics

Absorption

Hyoscine is poorly absorbed after oral administration; the bioavailability is 10% by this route. The drug is well absorbed following subcutaneous or intramuscular administration.

Distribution

Hyoscine is 11% protein-bound in the plasma; the V_D is 2.0 l/kg.

Metabolism

The drug is extensively metabolized in liver and tissues to scopine and scopic acid.

Excretion

2% of an oral dose is excreted unchanged in the urine and 5% in the bile. The clearance is 45 l/hour and the elimination half-life is 2.5 hours.

Special points

The drug may induce acute clinical and biochemical manifestations in patients with porphyria.




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Susan Smith, Edward Scarth, and Martin Sasada

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I

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Imipramine

Uses

Imipramine is used for the treatment of:

1. depression and
2. nocturnal enuresis.

Chemical

A dibenzazepine derivative.

Presentation

As 10/25 mg tablets and a syrup containing 5 mg/ml of imipramine hydrochloride.

Main action

Antidepressant.

Mode of action

Tricyclic antidepressants may potentiate the action of biogenic amines within the central nervous system by preventing their re-uptake at nerve terminals. They also antagonize muscarinic cholinergic, alpha-1 adrenergic, and H1 and H2 histaminergic receptors.

Routes of administration/doses

The adult oral dose is 25–50 mg 6–8-hourly.

Effects

CVS

Imipramine causes postural hypotension as a result of peripheral alpha-adrenergic blockade; a compensatory tachycardia may develop. The tricyclic antidepressants are also negatively inotropic; they also have characteristic effects on ECG morphology, including T wave flattening and inversion.

RS

Imipramine has little effect on respiratory function when normal doses are used.

CNS

The predominant effect of the drug is an antidepressant action which may take several weeks to develop; sedation, weakness, and fatigue are also commonly produced.

AS

High doses of imipramine increase the gastric emptying time.

Metabolic/other

The drug may produce excessive sweating by an unknown mechanism.

Toxicity/side effects

Occur in 5% and include palpitations, dysrhythmias, tremor, confusion, mania, and hepatic dysfunction. Anticholinergic side effects (blurred vision, dryness of the mouth, constipation, and urinary retention) may also occur. Overdose of the drug may result in fits, coma, and fatal dysrhythmias.

Kinetics

Absorption

The drug is well absorbed when administered orally; the bioavailability is 19–35%.



Distribution



Imipramine is 95% protein-bound in the plasma; the V_D is 15–31 l/kg.

Metabolism

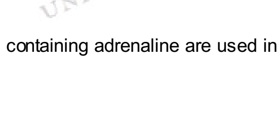
The drug is demethylated to an active form, desimipramine; this is inactivated by hydroxylation with subsequent conjugation to glucuronide.

Excretion

The glucuronide conjugates are excreted in the urine. The clearance is 11–19 ml/min/kg and the elimination half-life is 11–25 hours.

Special points

Scopolamine and the phenothiazines displace tricyclic antidepressants from their binding sites on plasma proteins and thus increase the activity of the latter; barbiturates increase the rate of hepatic metabolism of tricyclic antidepressants and decrease their activity.



Imipramine accentuates the cardiovascular effects of adrenaline; care should be exercised when local anaesthetic agents containing adrenaline are used in patients receiving the drug. Imipramine also increases the likelihood of dysrhythmias occurring during general anaesthesia.

Imipramine is not removed by haemodialysis.

Insulin

Uses



Insulin is used in the management of:



1. type I diabetes mellitus
2. diabetic emergencies
3. the perioperative control of blood sugar concentration
4. hyperkalaemia and
5. to improve glucose utilization during total parenteral nutrition and
6. in provocation tests for growth hormone.

Chemical

A polypeptide hormone. Human insulin is produced commercially by recombinant DNA techniques; bovine insulin differs by three and porcine insulin by one amino acid from human insulin.

Presentation

A wide variety of insulin preparations are available; the standard preparations contain 100 units/ml. The source may be human recombinant, bovine, or porcine and each may be modified by the addition of zinc or protamine to retard absorption.

Main actions

Stimulation of carbohydrate metabolism, protein synthesis, and lipogenesis.

Mode of action

Insulin binds to and activates a specific membrane-bound receptor; the effects of this may be mediated by alterations in the intracellular concentrations of cyclic nucleotides. Insulin exerts a direct effect on lipoprotein lipase, increases the rate of transcriptional and translational events during protein synthesis, and controls membrane polarization and ion transport by activating $Na^{+}K^{+}$ATPase.

Routes of administration/doses

Insulin may be administered intravenously, intramuscularly, and subcutaneously in a dose titrated according to the blood sugar estimations. It may be diluted for intravenous infusion in saline/glucose. The apparent dose requirement is increased by 20% when bovine or porcine insulin is used in place of human insulin.

Rapidly acting insulins act within 1 hour and have duration of action of 5–7 hours; slow-acting preparations act within 4 hours and have duration of action of 18–36 hours.

Continuous insulin infusion devices are also available for patients.

Effects

Metabolic/other

Insulin has profound effects upon carbohydrate, fat, and protein metabolism. The drug increases the rate of diffusion of glucose into all cells and specifically into hepatocytes by enhancing the activity of glucokinase (which causes the initial phosphorylation of glucose, thereby 'trapping' glucose intracellularly). The drug increases the rate of glycogen synthesis by enhancing the activity of phosphofructokinase (which is involved in glucose phosphorylation) and glycogen synthetase (which polymerizes monosaccharides to form glycogen). Insulin simultaneously inhibits glycogenolysis by an action on phosphorylase and inhibits gluconeogenesis. It also facilitates diffusion of glucose into muscle cells.

Insulin causes fat deposition in adipose tissue by increasing the hepatic synthesis of fatty acids; these are utilized within the liver to form triglycerides which are released into the bloodstream; insulin simultaneously activates lipoprotein lipase in adipose tissue which splits triglycerides into fatty acids, enabling them to be absorbed into adipose tissue where they are stored. The drug also inhibits a hormone-sensitive lipase, thereby preventing hydrolysis of triglycerides, and facilitates glucose transport into fat cells, leading to an increased supply of glycerol which is used in the manufacture of storage triglycerides.

Insulin causes active transport of amino acids into cells and increases mRNA translation and DNA transcription; in addition, it inhibits the catabolism of proteins.

The drug also causes an increase in the rate of potassium and magnesium transport into cells.

Toxicity/side effects

The commonest acute side effect of insulin is hypoglycaemia. Chronic use may be complicated by localized allergic reactions, lipodystrophy, and insulin resistance due to antibody formation.

Kinetics

Absorption

Insulin is inactive when administered orally since it is destroyed by gastrointestinal proteases.

Distribution

The drug exhibits little protein-binding; the V_D is 0.075 l/kg (0.146 l/kg in the diabetic subject).

Metabolism

Insulin is rapidly metabolized in liver, muscle, and kidney by glutathione insulin transhydrogenase.

Excretion

The metabolites appear in the urine. The clearance is 33.3 ml/min/kg (18.5 ml/min/kg in the diabetic subject) and the elimination half-life is 1.6–3.4 minutes (5.3–7.8 minutes in the diabetic subject).

Special points

The co-administration of steroids, levothyroxine, thiazide diuretics, and sympathomimetic agents tend to counteract the effects of insulin on carbohydrate metabolism. Many regimes of insulin administration have been described for the perioperative management of diabetic patients.

Insulin is not removed by dialysis.

Tight blood sugar control in critical illness has been shown to decrease mortality, especially in surgical patients.

Intralipid® 20%

Uses

Intralipid® 20% is used:

1. in the preparation of total parenteral nutrition (TPN) mixtures
2. in the treatment of local anaesthetic toxicity with or without circulatory arrest and
3. in the prevention of essential fatty acid deficiency syndrome.

Chemical

A fat emulsion.

Presentation

As a white, oil-water emulsion containing 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, sodium hydroxide, and water. It has a pH of approximately 8 and contains emulsified fat particles of 0.5 microns in size. Soybean oil consists of long chain unsaturated fatty acids in the following proportions: linoleic (44–62%), oleic (19–30%), palmitic (7–14%), linolenic (4–11%), stearic (1.4–5.5%). Intralipid® 20% has an osmolality of approximately 350 mOsm/kg water equivalent to 260 mOsm/l of emulsion.

Main action

As an energy substrate. Intralipid® 20% appears to reverse local anaesthetic cardiotoxicity.

Mode of action

The mechanism of action remains to be fully elucidated, but may involve the establishment of a concentration gradient away from the primary site of action of the local anaesthetic.

Route of administration/doses

Intralipid® 20% is administered by intravenous infusion when given as part of TPN therapy. The various doses with regard to this indication are beyond the scope of this book. For the treatment of local anaesthetic toxicity with or without circulatory arrest, together with advanced life support measures as indicated, an initial intravenous bolus dose of 1.5

ml/kg should be administered over 1 minute together with the commencement of an intravenous infusion at 15 ml/kg/hour. If cardiovascular stability has not been achieved or circulation deteriorates further, two subsequent bolus doses may be given 5 minutes apart. The continuous infusion rate should be doubled to 30 ml/kg/hour at any point after 5 minutes if identical criteria are met. The maximum cumulative dose is 12 ml/kg.

Effects

Metabolic/other

The principal effect of the drug is to act as an energy substrate, 2 kCal/ml, resulting in an increase in heat production and oxygen consumption.

Toxicity/side effects

Pancreatitis may occur secondary to hyperlipidaemia following administration of the drug. Hepatic dysfunction has been described after prolonged use.

Kinetics

Data are incomplete. The emulsified fat particles are cleared from the bloodstream by a mechanism thought to be similar to the removal of chylomicrons.

Special points

Following the administration of Intralipid® 20% (or another intravenous lipid emulsion) in the management of suspected local anaesthetic toxicity, serum amylase or lipase should be monitored for 2 days to assist in excluding the development of pancreatitis. Cases should be reported to the appropriate national regulatory organization governing patient safety (in the UK, this is the National Patient Safety Agency) and the use of lipid reported to the international registry at www.lipidregistry.org.

Ipratropium

Uses

Ipratropium is used in the treatment of asthma and chronic obstructive airways disease.

Chemical

A synthetic quaternary ammonium compound which is a derivative of atropine.

Presentation

As an isotonic solution of ipratropium bromide containing 0.25 mg/ml for nebulization or as a metered-dose aerosol delivering 200 micrograms/dose (18 micrograms of which is available to the patient).

Main action

Bronchodilatation.

Mode of action

Ipratropium acts by competitive inhibition of cholinergic receptors on bronchial smooth muscle, thereby blocking the bronchoconstrictor action of vagal efferent impulses. It may also inhibit acetylcholine enhancement of mediator release by blocking cholinergic receptors on the surface of mast cells.

Routes of administration/doses

The drug is administered by inhalation of a nebulized solution or aerosol in an adult dose of 100–500 micrograms 6-hourly or 1–2 puffs 6-hourly, respectively. The maximum effect is achieved in 1.5–2 hours and lasts 4–6 hours.

Effects

CVS

No effect on cardiovascular function is observed after administration by inhalation. When administered intravenously, tachycardia with an increase in blood pressure and cardiac output and a fall in central venous pressure may result.

RS

Bronchodilatation is the principal effect of the drug. No effect is seen on the viscosity or volume of secretions or the effectiveness of mucociliary clearance. The oxygen saturation remains unaltered following the administration of ipratropium.

CNS

The drug has no effect since ipratropium is unable to cross the blood–brain barrier.

AS

When given orally in large doses, gastric secretion and salivation are decreased by the drug.

Toxicity/side effects

None of the typical anticholinergic side effects is observed if ipratropium is administered by inhalation. 20–30% of patients receiving the drug experience transient local effects: dryness or unpleasant taste in the mouth. Local deposition of the nebulized drug on the eye may cause mydriasis and difficulty with accommodation.

Kinetics

Absorption

The bioavailability of the drug when administered orally is 3–30% and 5% by the inhaled route.



Distribution

The V_D is 0.4 l/kg.

Metabolism

Ipratropium is metabolized to 8 inactive metabolites.

Excretion

Occurs in approximately equal proportions in the urine and faeces. The clearance is 11.8 l/hour and the elimination half-life is 3.2–3.8 hours.

Special points

Ipratropium is less effective than beta-adrenergic agonists in the treatment of asthma although its effectiveness in the treatment of bronchitis appears to be equal to that of the beta-adrenergic agonists. An additive effect with the latter drugs is difficult to prove.

Isoflurane

Uses

Isofl urane is used:

1. for the induction and maintenance of general anaesthesia and has been used
2. for sedation during intensive care.

Chemical

A halogenated methyl ether which is a structural isomer of enflurane.

Presentation

As a clear, colourless liquid with a pungent smell which is non-flammable; the commercial preparation contains no additives or stabilisers and is supplied in amber coloured bottles. The molecular weight of isoflurane is 184.5, the boiling point is 48.5°C and the saturated vapour pressure is 32kPa at 20°C. The MAC of isoflurane is 1.15 (0.50 in 70% nitrous oxide) although is age dependant and ranges from 1.05 in elderly patients to 1.6 in neonates, the blood/gas partition coefficient is 1.4 and the fat/blood partition coefficient is 50. The oil:gas partition coefficient is 97.

Main Action

General anaesthesia (reversible loss of both awareness and recall of noxious stimuli).

Mode of Action

The mechanism of general anaesthesia remains to be fully elucidated. General anaesthetics appear to disrupt synaptic transmission (especially in the area of the ventrobasal thalamus). This mechanism may include potentiation of the GABA and glycine receptors and the antagonism at NMDA receptors. Their mode of action at the molecular level appears to involve expansion of hydrophobic regions in the neuronal membrane, either within the lipid phase or within hydrophobic sites in cell membranes.

Routes of Administration/Dose

Isoflurane is administered by inhalation; the agent has a pleasant, non-irritant odour. The concentration used for induction of anaesthesia is quoted as 5–8%. Maintenance of anaesthesia is usually achieved using between 0.5–3%.

Effects

CVS

Isoflurane causes a dose-related decrease in myocardial contractility and mean arterial pressure; systolic pressure decreases to a greater degree than diastolic pressure. The drug does not affect the heart rate and myocardial sensitisa-tion to catecholamines does not occur. The drug does not appear to cause the “coronary steal” phenomenon in man.

RS

Isoflurane is a respiratory depressant, causing dose-dependent decreases in tidal volume and an increase in respiratory rate. The drug depresses the ventilatory response to CO_2 and inhibits hypoxic pulmonary vasoconstriction. Isoflurane appears to relax bronchial smooth muscle constricted by histamine or acetylcholine.

CNS

The principle effect of isoflurane is general anaesthesia. The drug causes cerebral vasodilation, leading to an increase in cerebral blood flow; cerebral metabolic rate is decreased. As with other volatile anaesthetic agents, isoflurane may increase intra-cranial pressure in a dose-related manner. Isoflurane use is not associated with epileptiform activity.

GU

Isoflurane reduces renal blood flow and leads to an increase in fluoride ion concentrations (12µM to 90µM in anaesthesia lasting 1 to 6 hours respectively). There is no evidence that isoflurane causes gross changes in human renal function. The drug causes uterine relaxation.

Metabolic/Other

In animal models the drug decreases liver synthesis of fibrinogen, transferrin and albumin.

Toxicity/Side Effects

Isoflurane may cause PONV. Isoflurane is a trigger agent for the development of malignant hyperthermia. There are no reports of renal toxicity occurring in patients who have received the drug.

Kinetics

Absorption

The major factors affecting the uptake of volatile anaesthetic agents are solubility, cardiac output and the concentration gradient between the alveoli and venous blood. Due to the low blood/gas partition coefficient of isoflurane, it is exceptionally insoluble in blood; alveolar concentration therefore reaches inspired concentration very rapidly (fast wash in rate), resulting in a rapid induction of (and emergence from) anaesthesia. An increase in cardiac output increases the rate of alveolar uptake and slows the induction of anaesthesia. The concentration gradient between the alveoli and venous blood approaches zero at equilibrium; a large concentration gradient favours the onset of anaesthesia.

Distribution

The drug is initially distributed to organs with a high blood flow (brain, heart, liver, kidney) and later to less well-perfused organs (muscle, fat, bone).

Metabolism

0.2% of an administered dose undergoes hepatic metabolism, principally by oxidation and dehalogenation.

Excretion

Isoflurane is principally exhaled unchanged ; 0.2% of an administered dose is excreted in the urine as non-colatile fluorinated compounds.

Special Points

Isoflurane potentiates the action of co-administered depolarising and non-depolarising muscle relaxants to a greater extent than either halothane or enflurane.

As with other volatile anaesthetic agents, the co-administration of N_20, benzodiazepines, or opioids lowers the MAC of isoflurane.

Isoprenaline

Uses

Isoprenaline is used in the treatment of:

1. complete heart block (whilst awaiting transvenous pacing)
2. asthma
3. torsade de pointes and is used to provide
4. inotropic support.

Chemical

A synthetic catecholamine.

Presentation

As clear solutions for injection containing 0.02/1 mg/ml of isoprenaline hydrochloride. An aerosol delivering 80/400 micrograms of isoprenaline sulphate per metered dose is also available.

Main actions

Positive inotropism, positive chronotropism, and bronchodilatation.

Mode of action

Isoprenaline is a beta-adrenergic agonist; its actions are mediated by membrane-bound adenylate cyclase and the subsequent formation of cAMP.

Routes of administration/doses

Isoprenaline may also be administered as an infusion, diluted in water or 5% glucose, at the rate of 0.5–8 micrograms/min, according to response. The positive chronotropic effect becomes apparent after 20 minutes.

Effects

CVS

Isoprenaline is a powerful positive inotrope and chronotrope and thus causes an increase in the cardiac output and systolic blood pressure. The drug causes a decrease in the peripheral vascular resistance (a beta-2 effect); as a result, the diastolic blood pressure tends to decrease. The drug increases automaticity and enhances atrio-ventricular nodal conduction; it also increases coronary blood flow which tends to offset the increase in myocardial oxygen consumption that it produces.

RS

The drug is a potent bronchodilator and increases anatomical dead space and ventilation/perfusion mismatching which may lead to hypoxia.

CNS

Isoprenaline is a central nervous system stimulant.

AS

Isoprenaline decreases gastrointestinal tone and motility; the mesenteric blood supply is increased by the drug.

GU

The administration of isoprenaline reduces renal blood flow in normotensive subjects, but may increase renal perfusion in shock states. The drug also reduces uterine tone.

Metabolic/other

In common with adrenaline, isoprenaline increases the plasma concentration of free fatty acids and may cause hyperglycaemia. Isoprenaline inhibits antigen-induced histamine release and the formation of slow-releasing substance of anaphylaxis.

Toxicity/side effects

The use of isoprenaline may be complicated by excessive tachycardia, palpitations, angina, dysrhythmias, hypotension, and sweating. The use of isoprenaline inhalers by asthmatic patients has been associated with an excess mortality.

Kinetics

Quantitative data are lacking.

Absorption

The drug is well absorbed when administered orally, but is subject to an extensive first-pass metabolism in the intestinal mucosa and liver.

Distribution

Isoprenaline is 65% protein-bound in the plasma.

Metabolism

Isoprenaline is a relatively poor substrate for the action of monoamine oxidase; the drug is predominantly metabolized by catechol-O-methyltransferase in the liver to sulphated conjugates.

Excretion

15–75% of an administered dose of isoprenaline is excreted unchanged in the urine, the remainder as sulphated conjugates. The plasma half-life is 1–7 minutes.

Special points

Hypoxia, hypercapnia, and the co-administration of halothane, trilene, or cyclopropane increase the likelihood of the development of dysrhythmias during the use of isoprenaline. Tachyphylaxis may occur with prolonged use.







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Ketamine

Uses

Ketamine is used:

1. for the induction of anaesthesia, especially in poor-risk patients with hypotension or asthma
2. as a sole agent for short procedures such as change of burns dressings
3. for pre-hospital care and mass casualties
4. for analgesia both post-operatively and in patients receiving intensive care
5. for pain relief in patients with chronic pain and
6. for the reversal of severe unresponsive asthma.



Chemical

A phencyclidine derivative.

Presentation

Ketamine has a molecular weight of 238 and is presented as a colourless solution containing 10/50/100 mg/ml of racemic ketamine hydrochloride. It has a pH between 3.5–5.5 with a pKa of 7.5. The racemic mixture contains in equal proportions two enantiomers due to its chiral centre of the cyclohexanone ring ([S-(+)-ketamine] and [R-(–)-ketamine]). All preparations now contain 0.1 mg/ml benzethonium chloride as a preservative. S-(+)-ketamine is available in 5 and 25 mg/ml concentrations.

Main actions

Dissociative anaesthesia (a combination of profound analgesia with superficial sleep).

Mode of action

Ketamine is a non-competitive antagonist of the NMDA receptor Ca^{2+} channel pore and also inhibits NMDA receptor activity by interaction with the phencyclidine binding site. It reduces the pre-synaptic release of glutamate in addition to complex interactions with opioid receptors. There is some evidence suggesting that ketamine acts as an antagonist at monaminergic, muscarinic, and nicotinic receptors. Ketamine has local anaesthetic activity at high doses which may be the result of sodium channel inhibition.

S-(+)-ketamine has four times greater affinity for the NMDA receptor than R-(–)-ketamine. It is twice as potent as the racemic mixture and three times as potent as the R(–) form.

Routes of administration/doses

The intramuscular dose for induction of anaesthesia is 4–10 mg/kg; the onset of action is 2–8 minutes and the duration of action is 10–20 minutes. The corresponding intravenous dose is 0.5–2 mg/kg administered over a period of 60 seconds; the onset of action occurs within 30 seconds and the duration of action is 5–10 minutes. Ketamine may be used for maintenance of anaesthesia using an intravenous infusion at a rate of between 10–50 micrograms/kg/min. For sedation and analgesia an intramuscular dose of 2–4 mg/kg or intravenous dose of 0.2–0.75 mg/kg may used followed by an infusion of 5–20 micrograms/kg/min. Ketamine may also be administered orally, rectally, nasally, intrathecally, or extradurally. When used neuroaxially, the preservative-free solution must be used (not currently produced in the UK). Tolerance develops with repeated drug exposure.

Effects

CVS

Ketamine causes tachycardia and an increase in the blood pressure, central venous pressure, and cardiac output secondary to an increase in sympathetic tone. These effects mask the mild direct myocardial depressant effect ketamine exerts (reduced effect with S-(+)-ketamine). Baroreceptor function is well maintained and dysrhythmias are uncommon.

RS

Ketamine causes mild stimulation of respiration with relative preservation of airway reflexes. It acts as a bronchial smooth muscle relaxant and improves pulmonary compliance. The R-(–) isomer has greater activity against acetylcholine bronchial smooth muscle contraction compared with the S-(+) form. Therefore, the racemic mixture may be a more suitable choice in patients with bronchospasm.

CNS

The dissociative state may be produced by separation functionally and electrophysiologically of the thalamo-neocortical and limbic systems. The eyes remain open, pupillary dilatation and nystagmus occur, and hypertonus occurs. Cerebral blood flow, cerebral metabolic rate, intracranial pressure, and intraocular pressure are all increased. Visceral pain is poorly obtunded by ketamine. The EEG demonstrates dominant theta activity with loss of the alpha rhythm. S-(+) ketamine has a faster recovery time.

AS

Salivary secretions are increased. Gastric motility is unaffected.

GU

Ketamine increases uterine tone.

Metabolic/other

Circulating levels of adrenaline and noradrenaline are increased. Ketamine significantly reduces leukocyte activation during sepsis or hypoxaemia and *in vitro* tests suggest it suppresses pro-inflammatory cytokine production.

Toxicity/side effects

Post-operative nausea and vomiting are common. Transient rashes occur in 15% of patients. Emergence delirium, unpleasant dreams, and hallucinations are common, but may be alleviated by the use of a benzodiazepine premed. Pain on injection (especially intramuscularly) can be reduced by combination with lidocaine. Bladder dysfunction is reported in chronic abusers.

Kinetics

Absorption

The bioavailability of ketamine is: 20–25% (oral), 25–50% (nasal), and 93% (intramuscular).

Distribution

Ketamine is 20–50% protein-bound in the plasma; the V_D is 3 l/kg. The distribution half-life is 11 minutes. Recovery occurs due to redistribution across lipid membranes.

Metabolism

Ketamine is metabolized in the liver by N-demethylation and hydroxylation via the cytochrome P450 enzyme system of the cyclohexylamine ring. Norketamine, a metabolite which is 30% as potent as ketamine, is metabolized to an inactive glucuronide.

Excretion

The conjugated metabolites are excreted in the urine. The plasma clearance is 17 ml/kg/min and elimination half-life is 2.5 hours.

Special points

Antisialogogue premedication is recommended prior to the use of ketamine. Emergence phenomena are less frequent in the young and elderly. Premedication can reduce the incidence of these reactions as does leaving the patient in an undisturbed state during the recovery phase. Low-dose ketamine reduces tourniquet hypertension under general anaesthesia. Ketamine reduces inotropic requirements in septic patients. In animal models of endotoxic shock, ketamine reduces pulmonary drainage by enhancing haemodynamic stability and reducing pulmonary hypertension and extravasation. Ketamine may be harmful in patients with limited right ventricular reserve and increased pulmonary vascular resistance. Ketamine and thiopental are incompatible. Ketamine is a drug of misuse and is a class C drug in the UK.







Oxford Medicine







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Susan Smith, Edward Scarth, and Martin Sasada



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Labetalol

Uses

Labetalol is used in the treatment of:

1. all grades of hypertension
2. hypertensive emergencies and has been used
3. to produce controlled hypotension during anaesthesia
4. for the control of the reflex cardiovascular responses to intubation and
5. in the management of acute myocardial infarction.

Chemical



A synthetic salicylamide derivative.

Presentation

As a clear solution for injection containing 5 mg/ml and as 50/100/200/400 mg tablets of labetalol hydrochloride.

Main action

Antihypertensive.

Mode of action

Labetalol acts by selective antagonism of alpha-1, beta-1, and beta-2 adrenoceptors (the ratio of alpha: beta effects is 1:3 when administered orally and 1:7 when administered intravenously). The drug has some intrinsic sympathomimetic activity at beta-2 adrenoceptors and may cause some vasodilation directly by stimulation of beta-2 receptors in vascular smooth muscle.

Routes of administration/doses

The adult oral dose is 100–800 mg 12-hourly. The drug may also be administered intravenously as a 5–20 mg bolus injected over 2 minutes, with subsequent increments to a maximum adult dose of 200 mg or by infusion (diluted in glucose or glucose saline) at the rate of 20–160 mg/hour. When administered intravenously, labetalol acts in 5–30 minutes and has a mean duration of action of 50 minutes.

Patients should remain supine whilst receiving the drug via the intravenous route and subsequently assume the upright position cautiously as profound postural hypotension may occur.

Effects

CVS

Intravenous labetalol causes a 20% (greater in hypertensive patients) decrease in the systolic and diastolic blood pressure; the heart rate and cardiac output may decrease by 10%. The drug reduces the systemic vascular resistance by 14%; limb blood flow increases and coronary vascular resistance may decrease. Labetalol inhibits platelet aggregation *in vitro*.

RS

With single doses, the drug has no effect on FEV1, FVC, or specific airways resistance in patients with obstructive airways disease. Chronic use of the drug has no clinically significant effect on respiratory function.

CNS

Labetalol has no effect on cerebral blood flow; autoregulation is well maintained.

GU

Labetalol decreases renal vascular resistance by 20%, leading to an increase in renal blood flow. The glomerular filtration rate, however, remains unchanged.

Metabolic/other

The concentrations of adrenaline, noradrenaline, and prolactin increase acutely in hypertensive patients given labetalol intravenously. The drug may also decrease plasma renin activity and the concentration of angiotensin II. The ESR and serum transaminase concentration may increase following the administration of the drug; labetalol has no effect on plasma lipid concentration.

Toxicity/side effects

The side effects of beta-blockade (asthma, Raynaud's phenomenon, heart failure, cramps, nightmares, etc.) occur less frequently during the use of labetalol than do the side effects of alpha-blockade (dizziness, formication, nasal congestion, etc.). Gastrointestinal disturbances may also complicate the use of labetalol.

Kinetics

Absorption

Labetalol is rapidly absorbed when administered orally, but due to a significant first-pass metabolism, the bioavailability shows an eight-fold variation (11–86%).

Distribution

The drug is 50% protein-bound in the plasma; the V_D is 2.5–15.7 l/kg.

Metabolism

Labetalol is extensively metabolized in the liver (and possibly in the gut wall) to several inactive conjugates.

Excretion

Occurs predominantly as inactive conjugates in the urine (5% is excreted unchanged) with some appearing in the faeces. The clearance is 13–31 ml/min/kg and the elimination half-life is 3–8 hours. Renal impairment has no effect on the kinetics of labetalol; the dose should be reduced in the presence of hepatic impairment.

Special points

In the presence of concentrations of halothane 3%, labetalol causes a significant decrease in cardiac output, stroke volume, mean arterial pressure, and central venous pressure.

Haemodialysis will remove 1% of a dose of labetalol.

Levosimendan

Uses

Levosimendan is used in the treatment of acute heart failure syndromes resulting from a variety of aetiologies.

Chemical

A propanedinitrile derivative.

Presentation

As a clear, yellow, or orange solution for injection containing 2.5 mg/ml of levosimendan in 5 and 10 ml ampoules which needs to be diluted prior to administration.

Main action

Positive inotrope and vasodilatation.

Mode of action

Levosimendan increases calcium sensitivity by binding to myocardial troponin C, leading to stabilization and increased duration of calcium binding. This results in increased myocardial contractility without impairment of myocardial relaxation or increased oxygen demand. The drug also stimulates ATP-sensitive K^+ channels, leading to vasodilatation in addition to myocardial anti-stunning/ischaemic effects.

Route of administration/doses

Levosimendan is administered by intravenous infusion either by peripheral or central routes. An initial loading dose of 6–12 micrograms/kg should be administered over a 10-minute period followed by an intravenous infusion at a rate of 0.1–0.2 micrograms/kg/min.

Effects

CVS

The primary action of levosimendan is to increase myocardial contractility via increased calcium sensitivity without a corresponding increase in myocardial oxygen demand. The drug also causes coronary and peripheral vasodilatation. This may lead to anti-stunning and anti-ischaemia myocardial effects.

GU

The urine output and glomerular filtration rate increase, secondary to the increase in cardiac output.

Metabolic/other

Human data have demonstrated a reduction in lactate concentrations following administration of the drug in patients with septic shock.

Toxicity/side effects

Hypotension, headache, nausea, and vomiting are the commonest side effects reported, secondary to the vasodilatory effects of the drug. Hypokalaemia and arrhythmias have also been reported in small numbers of patients.

Kinetics

Distribution

Levosimendan is 97–98% bound to albumin; the V_D at steady state is 0.2 l/kg.

Metabolism

95% of an administered dose undergoes hepatic conjugation to cyclic or N-acetylated cysteinylglycine and cysteine conjugates.

5% of administered levosimendan undergoes intestinal reduction to aminophenylpyridazinone (OR-1855), followed by reabsorption into the plasma where further metabolism occurs by N-acetyltransferase to the active metabolite, OR-1896. The rate of metabolism of the drug is genetically determined although there is no evidence that any clinically significant therapeutic effect occurs between individuals who are rapid or slow acetylators. Levosimendan does not induce or inhibit the cytochrome P450 isoenzyme system.

Excretion

54% of an administered dose is renally excreted and 44% is found in the faeces. The elimination half-life is approximately 3 hours and the clearance is 3 ml/kg/hour. Less than 0.05% of levosimendan is excreted unchanged in the urine. The circulating metabolites (OR-1855 and OR-1896) are formed and excreted in a delayed pharmacokinetic profile, reaching a peak plasma concentration approximately 2 days after termination of an infusion of the drug. The metabolites of levosimendan have a half-life of 75–80 hours and are excreted predominantly in the urine.

Special points

The drug is not removed by haemodialysis.

Levosimendan may produce a clinical improvement which continues beyond the termination of the treatment period.

There are human data to suggest that administration of the drug may lead to reduced levels of circulating pro-inflammatory cytokines (IL-6) and soluble apoptosis mediators, in addition to lower concentrations of B-type natriuretic peptide.

Levothyroxine

Uses

Thyroid hormones are used in the treatment of:

1. hypothyroidism
2. myxoedema coma and
3. goitre.

Chemical

Both hormones are iodine-containing amino acid derivatives of thyronine.

Presentation

Levothyroxine is presented as tablets containing 25/50/100 micrograms of levothyroxine sodium. Triiodothyronine is presented as 20 micrograms tablets and a white lyophilized powder for reconstitution in water containing 20 micrograms of triiodothyronine.

Main action

Modulation of growth and metabolism.

Mode of action

The thyroid hormones, probably predominantly triiodothyronine, combine with a ‘receptor protein’ within the cell nucleus and thereby activate the DNA transcription process, leading to an increase in the rate of RNA synthesis and a generalized increase in protein synthesis.

Route of administration/doses

The adult oral dose of levothyroxine is 25–300 micrograms daily in divided doses, titrated according to the clinical response and results of thyroid function tests. The corresponding dose of triiodothyronine is 10–60 micrograms daily; the dose by the intravenous route is 5–20 micrograms 4–12-hourly; close monitoring is essential during intravenous administration. There is a 24-hour latency period before the effects of levothyroxine are manifested; the peak effect occurs in 6–7 days. Triiodothyronine acts in 6 hours and the peak effect is observed within 24 hours.

Effects

CVS

The thyroid hormones are positively inotropic and chronotropic; these effects may be mediated by an increase in the number of myocardial beta-adrenergic receptors. The systolic blood pressure is increased by 10–20 mmHg; the diastolic blood pressure decreases and mean arterial pressure remains unchanged. Vasodilation results from the increase in peripheral oxygen consumption; the circulating blood volume also increases slightly.

RS

The thyroid hormones increase the rate and depth of respiration, secondary to the increase in the basal metabolic rate.

CNS

The hormones have a stimulatory effect on central nervous system function; tremor and hyperreflexia may result. Their physiological function also includes mediation of negative feedback on the release of thyroid-stimulating hormone from the pituitary.

AS

Appetite is increased following the administration of levothyroxine or triiodothyronine; the secretory activity and motility of the gastrointestinal tract are also increased.

GU

The thyroid hormones are involved in the control of sexual function and menstruation.

Metabolic/other

Thyroid hormones promote gluconeogenesis and increase the mobilization of glycogen stores. Lipolysis is stimulated, leading to an increase in the concentration of free fatty acids; hypercholesterolaemia may result from increased cholesterol turnover. The rate of protein synthesis is enhanced.

Toxicity/side effects

Excessive administration of the thyroid hormones results in the clinical state of thyrotoxicosis.

Kinetics

Absorption

Both levothyroxine and triiodothyronine are completely absorbed when administered orally.

Distribution

Both hormones are bound to thyroid-binding globulin and thyroid-binding pre-albumin in the plasma; levothyroxine is 99.97% bound and triiodothyronine is 99.5% bound. The V_D of levothyroxine is 0.2 l/kg and that of triiodothyronine is 0.5 l/kg.

Metabolism

35% of levothyroxine is converted to triiodothyronine in the periphery (predominantly in the liver and kidney) and some to inactive reverse T3. Both levothyroxine and triiodothyronine undergo conjugation to glucuronide and sulphate and are excreted in the bile; some enterohepatic circulation occurs.

Excretion

20–40% of an administered dose is excreted in the faeces unchanged. The clearance of levothyroxine is 1.7 ml/min and the elimination half-life is 6–7 days; the clearance of triiodothyronine is 17 ml/min and the elimination half-life is 2 days.

Special points

The thyroid hormones increase the anticoagulant activity of co-administered warfarin. Beta-adrenergic antagonists interfere with the conversion of levothyroxine to triiodothyronine and lead to a relative increase in the inactive reverse T3 fraction.

Lidocaine

Uses

Lidocaine is used:

1. as a local anaesthetic and
2. in the treatment of ventricular tachydysrhythmias acting as a class Ib antiarrhythmic.

Chemical

A tertiary amine which is an amide derivative of diethylaminacetic acid.

Presentation

As a clear, colourless solution in concentrations of 0.5/1/1.5/2% solution of lidocaine hydrochloride (with or without 1: 200 000 adrenaline); a gel containing of 21.4 mg/ml of lidocaine hydrochloride (with or without chlorhexidine gluconate); a 5% ointment, a 10% spray, and a 4% aqueous solution for topical application; and as a cream/suppositories (in combination with hydrocortisone) for rectal administration. The 1% and 2% preparations are available with or without the preservatives, methylhydroxybenzoate (1.7 mg/ml) and propylhydroxybenzoate (0.3 mg/ml). Hydrochloric acid and sodium hydroxide are also present in some formulations (the latter to a maximum of 1%). The pKa of lidocaine is 7.7 and is 25% unionized at a pH of 7.4. The heptane:buffer partition coefficient is 2.9.

Main action

Local anaesthetic.

Mode of action

Local anaesthetics diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels; here they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the cell membrane.

Routes of administration/doses

Lidocaine may be administered topically, by infiltration, intrathecally, or epidurally; the toxic dose of lidocaine is 3 mg/kg (7 mg/kg with adrenaline). The maximum dose is 300 mg (500 mg with adrenaline). The adult intravenous dose for the treatment of acute ventricular dysrhythmias is a bolus injection of 1 mg/kg, administered over 2 minutes. A second dose may be administered according to the response of the patient. This is normally followed by an infusion at a rate of 20–50 micrograms/kg/min. Lidocaine acts in 2–20 minutes (dependent on the rate of administration and the presence of vasoconstrictors and the concentrations used). The speed of onset of lidocaine may be increased by the addition of bicarbonate to increase the pH of the solution, thereby increasing the unionized fraction of drug. The pH of the drug is approximately 6.4.

Effects

CVS

In low concentrations, lidocaine decreases the rate of rise phase 0 of the cardiac action potential by blockade of inactivated sodium channels. This results in a rise in the threshold potential with the duration of the action potential and effective refractory period being shortened. It has few haemodynamic effects when used in low doses except to cause a slight increase in systemic vascular resistance, leading to a mild increase in the blood pressure. In toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility, producing hypotension and, possibly, cardiovascular collapse.

RS

The drug causes bronchodilatation at subtoxic concentrations. Respiratory depression occurs in the toxic dose range.

CNS

The principal effect of lidocaine is reversible neural blockade; this leads to a characteristically biphasic effect in the central nervous system. Initially, excitation (lightheadedness, dizziness, visual and auditory disturbances, and seizure activity) occurs due to inhibition of inhibitory interneuron pathways in the cortex. With increasing doses, depression of both facilitatory and inhibitory pathways occurs, leading to central nervous system depression (drowsiness, disorientation, and coma). Local anaesthetic agents block neuromuscular transmission when administered intraneurally; it is thought that a complex of neurotransmitter, receptor, and local anaesthetic is formed, which has negligible conductance.

AS

Local anaesthetics depress contraction of the intact bowel.

Metabolic/other

Lidocaine may have some anticholinergic and antihistaminergic activity.

Toxicity/side effects

Lidocaine is intrinsically less toxic than bupivacaine. Allergic reactions to the amide-type local anaesthetic agents are extremely rare. The side effects are predominantly correlated with excessive plasma concentrations of the drug, as described above. Methaemoglobinaemia may occur if doses in excess of 600 mg are used and is caused by a metabolite, O-toluidine, although this condition may occur at lower doses in patients suffering from anaemia, a haemoglobinopathy, or in patients receiving therapy known to also precipitate methaemoglobinaemia (sulphonamides). Use of lidocaine for paracervical block or pudendal nerve block in obstetric patients is not recommended as this may give rise to methaemoglobinaemia in the neonate as the erythrocytes are deficient in methaemoglobin reductase.

Kinetics

Absorption

The absorption of local anaesthetic agents is related to:

1. the site of injection (intercostal > caudal > epidural > brachial plexus > subcutaneous)
2. the dose—a linear relationship exists between the total dose and the peak blood concentrations achieved and
3. the presence of vasoconstrictors which delay absorption.

Distribution

Lidocaine is 64–70% protein-bound in the plasma, predominantly to alpha-1 acid glycoprotein; the V_D is 0.7–1.5 l/kg.

Metabolism

Lidocaine is metabolized in the liver by N-dealkylation with subsequent hydrolysis to monoethylglycine and xylidide. Monoethylglycine is further hydrolyzed whilst xylidide undergoes hydroxylation to 4-hydroxy-2,6-xylidine which is the main metabolite and excreted in the urine. Metabolites of lidocaine may lower the fit threshold, thereby potentiating seizure activity whilst others have some antiarrhythmic properties.

Excretion

Less than 10% of the dose is excreted unchanged in the urine. The clearance is 6.8–11.6 ml/min/kg and the elimination half-life is 90–110 minutes. The clearance is reduced in the presence of cardiac and hepatic failure.

Special points

The onset and duration of conduction blockade is related to the pKa, lipid solubility, and the extent of protein binding. A low pKa and high lipid solubility are associated with a

rapid onset time; a high degree of protein binding is associated with a long duration of action. Local anaesthetic agents significantly increase the duration of action of both depolarizing and non-depolarizing relaxants.

Due to the narrow therapeutic index of lidocaine, the plasma concentrations of the drug need to be monitored in patients with cardiac and hepatic impairment.

Lidocaine is not removed by haemodialysis.

Intravenous administration of lidocaine decreases nitrous oxide and halothane requirements by 10% and 28%, respectively.

EMLA® (Eutectic Mixture of Local Anaesthetics) is a white cream used to provide topical anaesthesia prior to venepuncture and has also been used to provide anaesthesia for split skin grafting. It contains 2.5% prilocaine and 2.5% lidocaine in an oil-water emulsion. When applied topically under an occlusive dressing, local anaesthesia is achieved after 1–2 hours and lasts for up to 5 hours. The preparation causes temporary blanching and oedema of the skin; detectable methaemoglobinaemia may also occur in the presence of excessive O-toluidine plasma levels as a metabolite of prilocaine.

Linezolid

Uses

Linezolid is used in the treatment of:

1. nosocomial and community-acquired pneumonia
2. complex skin and soft tissue infections and
3. MRSA infection and vancomycin-resistant *Enterococcus* (VRE).

Chemical

An oxazolidinone.

Presentation

As 600 mg tablets and a solution for intravenous administration containing 2 mg/ml of linezolid.

Main action

Antibacterial active against a wide range of Gram-positive organisms, particularly *Enterococcus*, *Streptococcus*, and *Staphylococcal* spp., and Gram-positive anaerobes, including *Clostridium perfringens*.

Mode of action

Linezolid inhibits bacterial protein synthesis by binding specifically to the 50S ribosomal subunit, thereby preventing initiation complex formation.

Routes of administration/doses

The adult oral and intravenous dose is 600 mg 12-hourly.

Toxicity/side effects

Headache, abnormalities of liver function tests, taste alteration, and gastrointestinal disturbances are common. Fertility may be affected reversibly. Skin and bleeding disorders, phlebitis, and pancreatitis may also occur.

Kinetics

Absorption

Linezolid is rapidly absorbed after oral administration and has an oral bioavailability approaching 100%.

Distribution

The drug is 31% protein-bound in the plasma; the V_D is 0.64 l/kg.

Metabolism

Linezolid is metabolized by oxidation to two inactive carboxylic acid metabolites.

Excretion

30% is excreted unchanged in the urine, the metabolites are excreted in the urine and faeces. The elimination half-life is 5 hours and the clearance 120 ml/min.

Special points

Linezolid is a reversible non-selective MAOI. It enhances the effects of ephedrine on the blood pressure.

Lithium

Uses

Lithium is used in the treatment of:

1. mania and hypomania and in the prophylaxis of
2. recurrent bipolar depression
3. recurrent affective disorders and
4. as an adjunct in the treatment of chronic pain of non-malignant origin.

Chemical

An alkali metal.

Presentation

As tablets containing 200/250/400/450 mg of lithium carbonate.

Main action

Antipsychotic.

Mode of action

The precise mode of action of lithium is unknown; it may act by stabilization of membranes or by alteration of central neurotransmitter function.

Routes of administration/doses

The adult oral dose is 0.4–1.2 g/day; serum levels should be monitored within 1 week of starting lithium and regularly thereafter as the drug has a narrow therapeutic index. The therapeutic level is 0.5–1.5 mmol/l.

Effects

CVS

Prolonged lithium therapy may lead to reversible ECG changes, especially T wave depression.

CNS

The drug has no effect on central nervous system function in normal subjects although an increase in muscle tone occurs commonly. Lithium appears to lower the seizure threshold in epileptics.

GU

Over one-third of patients receiving lithium develop polyuria and polydipsia due to antagonism of the effects of ADH.

Metabolic/other

With prolonged use of lithium, retention of sodium (secondary to an increase in aldosterone secretion) may occur, as may hypercalcaemia and hypermagnesaemia. The drug has mild insulin-like effects on carbohydrate metabolism.

Toxicity/side effects

At therapeutic serum levels, disturbances of thyroid function, weight gain, tremor, pretibial oedema, and allergic phenomena may occur. Excessive serum concentrations may result in nausea and vomiting, abdominal pain, diarrhoea, ataxia, convulsions, coma, dysrhythmias, and death. Nephrogenic diabetes insipidus occurs in 5–20% of patients on long-term lithium treatment.

Kinetics

Absorption

The drug is rapidly absorbed when administered orally; the bioavailability is 100%.

Distribution

Lithium exhibits no demonstrable protein binding in the plasma; the V_D is 0.45–1.13 l/kg.

Excretion

95% of a dose of lithium is excreted in the urine; the remainder in sweat. The clearance is 0.24–0.46 ml/min/kg and the elimination half-life is 14–30 hours.

Special points

Renal, cardiac, and thyroid function should be monitored regularly during lithium therapy. Co-administration of lithium and diazepam has been reported to lead to hypothermia; the drug may also increase the duration of action of both depolarizing and non-depolarizing relaxants.

The drug is removed by haemodialysis.

Lorazepam

Uses

Lorazepam is used:

1. in the short-term treatment of anxiety
2. as a hypnotic
3. in premedication and
4. for the treatment of status epilepticus.

Chemical

A hydroxybenzodiazepine.

Presentation

As 1/2.5 mg tablets and as a clear, colourless solution for injection containing 4 mg/ml of lorazepam.

Main actions

1. hypnosis
2. sedation
3. anxiolysis
4. anterograde amnesia
5. anticonvulsant and
6. muscular relaxation.

Mode of action

Benzodiazepines are thought to act via specific benzodiazepine receptors found at synapses throughout the central nervous system, but concentrated especially in the cortex and midbrain. Benzodiazepine receptors are closely linked with GABA receptors and appear to facilitate the activity of the latter. Activated GABA receptors open chloride ion channels which then either hyperpolarize or short-circuit the synaptic membrane.

Routes of administration/doses

The adult oral or sublingual dose is 1–4 mg/day in divided doses. The intravenous or intramuscular dose is 0.025–0.05 mg/kg; intramuscular injection is painful.

Effects

CVS

Lorazepam appears to have no direct cardiac effects.

RS

Mild respiratory depression occurs following the administration of the drug, which is of clinical significance only in patients with lung disease.

CNS

The drug produces sedation, anterograde amnesia, and an anticonvulsant effect.

AS

Lorazepam has no effect on basal gastric acid secretion, but decreases pentagastrin-stimulated gastric acid secretion by 25%.

Metabolic/other

Circulating cortisol and glucose levels fall when lorazepam is used in premedication, probably secondarily to its anxiolytic effect.

Toxicity/side effects

Drowsiness, sedation, confusion, and impaired coordination occur in a dose-dependent fashion. Paradoxical stimulation has been reported and occurs more frequently when hyoscine is administered concurrently. Tolerance and dependence may occur with prolonged use of benzodiazepines; acute withdrawal of benzodiazepines in these circumstances may produce insomnia, anxiety, confusion, psychosis, and perceptual disturbances.

Kinetics

Absorption

Lorazepam has a bioavailability of 90% when administered by the oral or intramuscular route.

Distribution

The drug is 88–92% protein-bound in the plasma; the V_D is 1 l/kg. Lorazepam is less extensively distributed than diazepam and thus has a longer duration of action despite the shorter elimination half-life of lorazepam.

Metabolism

Lorazepam is conjugated directly in the liver to glucuronide to form an inactive water-soluble metabolite.

Excretion

80% of an orally administered dose appears in the urine as the glucuronide. The clearance is 1 ml/min/kg and the elimination half-life is 8–25 hours—this is unaffected by renal disease.

Special points

The co-administration of cimetidine does not impair the metabolic clearance of lorazepam.

The drug is not removed by haemodialysis.





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Macrolides

Uses

Macrolides are used in the treatment of infections of:

1. the respiratory tract
2. skin, soft tissue, and bone
3. ocular, ear, and oral infections
4. gastrointestinal infections
5. genitourinary infections
6. surgical prophylaxis and
7. for the prophylaxis of subacute bacterial endocarditis
8. and have been used as a prokinetic in intensive care.

Chemical

A macrocyclic lactone ring to which deoxy sugars are attached.

Presentation

Macrolides in clinical use include erythromycin, clarithromycin, and azithromycin. Erythromycin is available in a form for topical use as a treatment for acne vulgaris, as a powder for oral suspension, in tablet and capsule formulations, and as an intravenous formulation. Clarithromycin is available as an oral preparation or for intravenous use. The drug is also available in combination with other agents for *Helicobacter pylori* eradication therapy. Azithromycin is available in tablet, oral suspension, or intravenous formulations.

Main action

Macrolides are bactericidal/bacteriostatic antibiotics that are active predominantly against:

1. Gram-positive bacteria
2. some Gram-negative bacteria (particularly with azithromycin)
3. Gram-positive and negative anaerobes
4. obligate intracellular parasites (*Legionella*, *Mycoplasma*).

Mode of action

Macrolides bind to specific bacterial ribosomal proteins (50S subunit) and inhibiting peptide translocase, thereby preventing the formation of polymerized peptides.

Route of administration/doses

Macrolides may be administered topically as creams or ointments, orally or intravenously, or via the intrathecal/intraventricular route. The specific dose, route, and frequency of an agent administered are dependent on the clinical indication, age of the patient, and particular agent being used. Doses should be reduced in patients with renal impairment.

Effects

AS

Erythromycin has a prokinetic effect on gut motility.

Toxicity/side effects

Common side effects include nausea, vomiting, and diarrhoea. Hepatic dysfunction, allergic phenomena, and ototoxicity have also been reported.

Kinetics

Absorption

Macrolides are absorbed to varying degrees depending on the specific agent: erythromycin (10–60%), clarithromycin (50%), azithromycin (37%). Erythromycin undergoes first-pass metabolism.

Distribution

The V_D for erythromycin is 0.34–1.22 l/kg and for azithromycin 0.44 l/kg. The percentage of drug bound to plasma proteins is 81–87% for erythromycin, 8% for clarithromycin, and 12–50% for azithromycin. High concentrations are found within the lung tissue. CSF is poorly penetrated by these agents.

Metabolism

Macrolides undergo hepatic metabolism in man. Erythromycin undergoes demethylation; clarithromycin is converted to 14-hydroxyclarithromycin as part of first-pass metabolism. This metabolite is microbiologically active. Clarithromycin is also metabolized in the liver via N-dealkylation. Azithromycin is metabolized via hepatic N- and O-demethylation to inactive metabolites.

Excretion

Erythromycin and clarithromycin are excreted renally. The clearance of erythromycin is 5–13.2 ml/min/kg, the half-life is 1.6 hours, with 2–15% of the drug being excreted unchanged in the urine. The clearance of clarithromycin is unknown as it exhibits non-linear kinetics, the half-life is 5–6 hours, with 33% of the drug being excreted unchanged in the urine and 11% as the 14-hydroxyclarithromycin metabolite. 10% of an administered dose of clarithromycin is excreted via the bile. Azithromycin has a clearance of 10.18 ml/kg/min, a prolonged half-life of 68 hours, with 12% of the drug being excreted unchanged in the urine. The major excretion pathway for azithromycin is via the bile.

Special points

Erythromycin and clarithromycin may cause QT prolongation in the critically ill. All macrolides inhibit CYP450 3A4, which may lead to increased drug levels of the following agents if administered concurrently to a patient: methylprednisolone, warfarin, phenytoin, ciclosporin, theophylline, sodium valproate, tacrolimus, midazolam, digoxin.

Erythromycin and clarithromycin are not removed by haemofiltration or dialysis and therefore, the dose should be halved in patients receiving renal replacement therapy. No dose adjustment is necessary for azithromycin.

Erythromycin should be avoided in patients with suspected or confirmed porphyria.

Antimicrobial agents should always be administered following consideration of local pharmacy and microbiological policies.

Magnesium

Uses

Magnesium has been used in the management of:

1. pre-eclampsia and eclampsia
2. hypomagnesaemia associated with malabsorption syndromes (especially chronic alcoholism), diuretics, and critical illness
3. premature labour (as a tocolytic)
4. acute myocardial infarction
5. torsade de pointes and other ventricular dysrhythmias
6. barium poisoning
7. asthma
8. cerebral oedema
9. spasms occurring with tetanus
10. autonomic hyperreflexia secondary to chronic spinal cord injury and is
11. a component of cardioplegic solutions.

Chemical

An inorganic sulphate.

Presentation

A clear, colourless solution of magnesium sulphate containing 2.03 mmol/ml of ionic magnesium 50%.

Main actions

Magnesium is an essential cofactor in over 300 enzyme systems. It is also essential for the production of ATP, DNA, RNA, and protein function.

Mode of action

The precise mechanism of the anticonvulsant activity of magnesium remains unknown; it produces a dose-dependent pre-synaptic inhibition of acetylcholine release at the neuromuscular junction.

Routes of administration/doses

Magnesium sulphate may be administered intravenously or intramuscularly. A number of dose regimes have been described for the use of magnesium sulphate in the

management of pre-eclampsia, e.g. 16 mmol administered intravenously over 20 minutes followed by an infusion of 4–8 mmol/hour. Serum concentrations should be monitored repeatedly and the dose adjusted correspondingly. Loss of deep tendon reflexes is a useful clinical sign of impending toxicity.

Effects

CVS

Magnesium acts peripherally to cause vasodilation and may cause hypotension when used in high doses. The drug slows the rate of sinoatrial node impulse formation and prolongs sinoatrial conduction time, the PR interval, and atrio-ventricular nodal effective refractory period. Magnesium attenuates both the vasoconstrictor and arrhythmogenic actions of adrenaline.

RS

Magnesium is an effective bronchodilator and attenuates hypoxic pulmonary vasoconstriction.

CNS

The drug is a CNS depressant and exhibits anticonvulsant properties. High concentrations inhibit catecholamine release from adrenergic nerve terminals and the adrenal medulla.

AS

Magnesium sulphate acts as an osmotic laxative when administered orally.

GU

The drug exerts a renal vasodilator and diuretic effect. It decreases uterine tone and contractility; placental perfusion may increase secondary to a decrease in uterine vascular resistance. Magnesium crosses the placenta and may cause neonatal hypotonia and neonatal depression.

Metabolic/other

Magnesium prolongs the clotting time of whole blood, decreases thromboxane B2 synthesis, and inhibits thrombin-induced platelet aggregation.

Toxicity/side effects

Minor side effects include warmth, flushing, nausea, headache, and dizziness. Dose-related side effects include somnolence, areflexia, atrio-ventricular and intraventricular conduction disorders, progressive muscular weakness, and cardiac arrest. The toxic effects can be reversed by the administration of calcium. Intramuscular injection of magnesium sulphate is painful.

Kinetics

Absorption

25–65% of ingested magnesium is absorbed.

Distribution

Magnesium is 30% protein-bound in the plasma.

Excretion

More than 50% of an exogenous magnesium load is excreted in the urine, even in the presence of significant magnesium deficiency.

Special points

Magnesium enhances the effects of other CNS depressants and neuromuscular blocking agents; 30–50% of the normal dose of non-depolarizing relaxants should be used to maintain neuromuscular blockade in the presence of magnesium sulphate. Acute administration of magnesium sulphate prior to the use of suxamethonium appears to prevent potassium release and may reduce the incidence and severity of muscle pains.

Magnesium deficiency is present in 20–65% of patients receiving intensive care.

Mannitol

Uses

Mannitol is used:

1. to reduce the pressure and volume of cerebrospinal fluid
2. to preserve renal function during the perioperative period in jaundiced patients and in those undergoing major vascular surgery
3. in the short-term management of patients with acute glaucoma
4. for bowel preparation prior to colorectal procedures
5. to initiate a diuresis in transplanted kidneys and
6. in the treatment of rhabdomyolysis.

Chemical

An alcohol, derived from *Dahlia* tubers.

Presentation

As sterile, pyrogen-free solutions of 10% and 20% mannitol in water; crystallization may occur at low temperatures.

Main actions

Osmotic diuresis and antioxidant.

Mode of action

Mannitol is a low molecular weight (182 Da) compound and is thus freely filtered at the glomerulus and not reabsorbed; neither does it cross the intact blood–brain barrier. Its action as a diuretic rests upon the fact that it increases the osmolality of the glomerular filtrate and tubular fluid, increasing urinary volume by an osmotic effect. Mannitol decreases CSF volume and pressure by:

1. decreasing the rate of CSF formation and
2. by withdrawing brain extracellular water across the blood–brain barrier into the plasma; if the barrier is disrupted, mannitol passes into the brain extravascular space and is ineffective.

Mannitol also acts as a hydroxyl radical scavenger.

Routes of administration/doses

For the reduction of elevated intracranial pressure, a dose of 1 g/kg is infused intravenously over 15 minutes prior to operative treatment. Subsequently, intermittent doses of 0.25–0.5 g/kg may be used for the treatment of persistently elevated intracranial pressure. The diuretic dose is 0.5–1 g/kg. Mannitol acts within a few minutes and lasts 1–4 hours.

The oral dose for bowel preparation is 100 ml of the 20% solution—care should be taken to maintain adequate hydration.

Effects

CVS

The acute administration of mannitol increases the cardiac output; blood pressure increases by 5–10 mmHg.

CNS

Mannitol induces a significant reduction in intracranial pressure with preservation of cerebral blood flow in patients with intact autoregulation; in patients with defective autoregulation, a minimal reduction in intracranial pressure with an increase in cerebral blood flow occurs.

GU

Renal blood flow is increased and the rate of renin secretion decreases; mannitol washes out the medullary interstitial gradient, leading to a decreased ability to produce concentrated urine. Diuresis occurs 1–3 hours after administration.

Metabolic/other

The plasma sodium and potassium concentrations may fall and urea increase with the use of high doses of mannitol.

Toxicity/side effects

Circulatory overload and rebound increases in intracranial pressure may occur following the use of mannitol. Allergic responses are rare; the drug is irritant to tissues and veins. Mannitol may have toxic effects on distal convoluted tubule and collecting duct cells, causing vacuolization.

Kinetics

Absorption

After oral administration, approximately 17.5% is absorbed in the small bowel.

Distribution

The drug shows a biphasic distribution to plasma and extracellular water; complex fluid shifts occur in response to this. The V_D is 0.47 l/kg.

Metabolism

Mannitol is not metabolized in man.

Excretion

The drug is excreted unchanged in the urine: the clearance is 7 ml/min/kg and the elimination half-life is 72 minutes.

Special points

Blood should not be co-administered with mannitol. A total dose exceeding 3 g/kg/day may produce a serum osmolality greater than 320 mOsm/l. Rebound increases in intracranial pressure may occur after the cessation of mannitol therapy.

Metaraminol

Uses

Metaraminol is used as an adjunct in the treatment of hypotension occurring during general or neuroaxial anaesthesia.

Chemical

A synthetic sympathomimetic amine.

Presentation

As a clear solution containing 10 mg/ml of metaraminol tartrate.

Main action

Peripheral vasoconstriction.

Mode of action

Metaraminol is a direct- and indirect-acting sympathomimetic agent that has agonist effects mainly at alpha-1-adrenoceptors, but also has some beta-adrenoceptor activity. The drug also causes noradrenaline to be released from intra-cytoplasmic stores in addition to causing adrenaline release.

Routes of administration/doses

The adult dose by intravenous infusion of metaraminol diluted in saline or glucose should be titrated according to response; bolus doses of 0.5–5 mg may be administered intravenously with extreme caution. The corresponding intramuscular or subcutaneous dose for the prevention of hypotension is 2–10 mg. The onset of effect after intravenous administration occurs within 1–2 minutes with maximum effect at 10 minutes and lasts 20–60 minutes. The onset of effect after intramuscular or subcutaneous administration occurs within 10 minutes and lasts 1–1.5 hours.

Effects

CVS

Metaraminol causes a sustained increase in the systolic and diastolic blood pressures due to an increase in the systemic vascular resistance; it also increases pulmonary vascular resistance. A reflex bradycardia occurs. The drug has positive inotropic properties although the cardiac output may fall due to the increase in systemic vascular resistance. Coronary blood flow is increased by metaraminol by an indirect mechanism.

RS

The drug causes a slight decrease in the respiratory rate and an increase in the tidal volume.

CNS

The cerebral blood flow is decreased by the administration of metaraminol.

GU

The renal blood flow is decreased by metaraminol and the drug causes contraction of the pregnant uterus and reduces uterine artery blood flow via its effect at alpha-adrenoceptors.

Metabolic/other

Metaraminol increases glycogenolysis and inhibits insulin release, leading to hyperglycaemia. Lipolysis is increased and the concentration of free fatty acids may become elevated. The drug may increase oxygen consumption and elevate body temperature.

Toxicity/side effects

Headaches, dizziness, tremor, nausea, and vomiting may occur with the use of the drug. Rapid and large increases in blood pressure resulting in left ventricular failure and cardiac arrest have been reported after the administration of metaraminol. Extravascular injection of the drug may lead to tissue necrosis and abscess formation at the injection site.

Excessive hypertension may occur when metaraminol is administered to patients with hyperthyroidism or those receiving monoamine oxidase inhibitors.

Kinetics

There is limited quantitative data available. The effect starts 1–2 minutes after intravenous injection, 10 minutes after intramuscular injection, and 5–20 minutes after subcutaneous injection. It is reportedly 45% protein-bound.

The drug does not cross the blood–brain barrier.

Metformin

Uses

Metformin is used in the treatment of non-insulin-dependent (type II) diabetes mellitus.

Chemical

A biguanide.

Presentation

As 500/850 mg tablets of metformin hydrochloride.

Main action

Hypoglycaemia.

Mode of action

Biguanides have no effect in the absence of circulating insulin; they do not alter insulin concentration, but do enhance its peripheral action. They appear to act by inhibiting the

intestinal absorption of glucose and decreasing the peripheral utilization of glucose, both by increasing the rate of anaerobic glycolysis and by decreasing the rate of gluconeogenesis.

Routes of administration/doses

The adult oral dose is 1.5–3 g daily in divided doses. Metformin has a duration of action of 8–12 hours.

Effects

CVS

Metformin reduces the intestinal absorption of glucose, folate, and vitamin B12; it has no effects on gastric motility. The drug may also increase the intestinal utilization of glucose and cause weight loss.

Metabolic/other

Metformin increases the sensitivity to the peripheral actions of insulin by increasing the number of low-affinity binding sites for insulin in red blood cells, adipocytes, hepatocytes, and skeletal muscle cells. The drug does not cause hypoglycaemia in diabetic subjects receiving metformin monotherapy. Metformin inhibits the metabolism of lactate and causes a decrease in the plasma triglyceride, cholesterol, and pre-beta lipoprotein concentrations.

Toxicity/side effects

Metformin is normally well tolerated; gastrointestinal disturbances may occur. Lactic acidosis may complicate the use of the drug rarely.

Kinetics

Absorption

The drug is slowly absorbed from the small intestine; the oral bioavailability is 50–60%.

Distribution

Metformin is not protein-bound in the plasma.

Metabolism

No metabolites of the drug have been detected in man.

Excretion

The drug is excreted essentially unchanged in the urine. The clearance exceeds the glomerular filtration rate, implying active tubular secretion. The elimination half-life is 1.7–4.5 hours. The drug is not recommended for use in patients with renal impairment.

Methohexital

Uses

Methohexital is used for the induction and maintenance of anaesthesia.

Chemical

A methylated oxybarbiturate.

Presentation

As a white, crystalline powder in vials containing 0.1/0.5 g of methohexital sodium mixed with sodium carbonate; this is dissolved in water before administration to yield a clear, colourless solution with a pH of 11 and a pKa of 7.9, which is stable in solution for 6 weeks.

Main action

Hypnotic.

Mode of action

Barbiturates are thought to act primarily at synapses by depressing post-synaptic sensitivity to neurotransmitters and by impairing pre-synaptic neurotransmitter release. Multi-synaptic pathways are depressed preferentially; the reticular activating system is particularly sensitive to the depressant effects of barbiturates. The action of barbiturates at the molecular level is unknown. They may act in a manner analogous to that of local anaesthetic agents by entering cell membranes in the unionized form, subsequently becoming ionized and exerting a membrane-stabilizing effect by decreasing sodium and potassium ion conductance, decreasing the amplitude of the action potential, and slowing the rate of conduction in excitable tissue. In high concentrations, barbiturates depress the enzymes involved in glucose oxidation, inhibit the formation of ATP, and depress calcium-dependent action potentials. They also inhibit calcium-dependent neurotransmitter release and enhance chloride ion conductance in the absence of GABA.

Routes of administration/doses

The drug is usually administered intravenously in a dose of 1–1.5 mg/kg; it acts in one arm–brain circulation time and awakening occurs in 2–3 minutes. The drug may also be administered intramuscularly in a dose of 6.6 mg/kg or rectally in a dose of 15–20 mg/kg.

Effects

CVS

Methohexital has negatively inotropic effects and decreases systemic vascular resistance; it may also depress transmission in autonomic ganglia and thus lead to hypotension.

RS

Methohexital is a more powerful respiratory depressant than thiopental and obtunds the ventilatory response to both hypoxia and hypercarbia. The drug may cause pronounced coughing and hiccuping.

CNS

At low doses, methohexital may cause paradoxical excitement. Induction of anaesthesia with the drug is associated with an increased incidence of excitatory phenomena when compared to thiopental. Methohexital decreases both the cerebral blood flow and intracranial pressure. The drug may cause epileptiform EEG patterns; abnormal muscle movements may also occur due to neurotransmitter release.

AS

The drug causes some depression of intestinal activity and constriction of the splanchnic vasculature.

GU

Methohexital decreases renal plasma flow and increases ADH secretion, leading to a decrease in urine output. It has no effect on the tone of the gravid uterus.

Metabolic/other

The drug decreases the production of superoxide anions by polymorphonuclear leucocytes.

Toxicity/side effects

Methohexital causes pain on injection in up to 80% of patients. It is less irritant than thiopental when extravasation occurs, but when administered intra-arterially, may lead to arterial constriction and thrombosis. Anaphylactoid reactions occur with a frequency similar to that observed with thiopental. Nausea and vomiting may complicate the use of methohexital.

Kinetics

Distribution

The drug is 51–65% protein-bound in the plasma, predominantly to albumin; 20% is sequestered in red blood cells; the V_D is 1.13 l/kg. The rapid onset of action of the drug is due to:

1. the high blood flow to the brain
2. the lipophilicity of the drug and
3. its low degree of ionization—only the non-ionized fraction crosses the blood–brain barrier (methohexital is 75% non-ionized at pH 7.4; hyperventilation increases the non-bound fraction and increases the anaesthetic effect). The relatively brief duration of anaesthesia following a bolus of methohexital is due to redistribution to muscle and later to fat. Methohexital has a shorter duration of action than thiopental due to its very short distribution half-life and a high clearance which is four times greater than that of thiopental.

Metabolism

Occurs in the liver, primarily to a 4-hydroxy metabolite.

Excretion

The metabolites are excreted in the urine, 1% of the dose is excreted unchanged. The clearance is 7.9–13.9 ml/min/kg and the elimination half-life is 1.8–6 hours.

Special points

The drug may induce acute clinical and biochemical manifestations in patients with porphyria and is also not recommended for use in epileptics. Methohexital should be used with caution in patients with fixed cardiac output states, hepatic or renal dysfunction, myxoedema, dystrophia myotonica, myasthenia gravis, familial periodic paralysis, and in the elderly or in patients who are hypovolaemic.

Methoxamine

Uses

Methoxamine is used for:

1. the correction or prevention of hypotension during spinal or general anaesthesia and cardiopulmonary bypass and
2. the treatment of supraventricular tachycardias.

Chemical

A synthetic sympathomimetic amine.

Presentation

As a clear solution containing 20 mg/ml of methoxamine hydrochloride.

Main actions

Peripheral vasoconstriction and bradycardia.

Mode of action

Methoxamine is a selective alpha-1 adrenergic agonist.

Routes of administration/doses

Methoxamine is administered intravenously at a rate of 1 mg/min to a total dose of 5–10 mg in an adult; it acts within 1–2 minutes and has a duration of action of 1 hour. The corresponding intramuscular dose is 5–20 mg when the onset of action is 15–20 minutes and duration of effect is 90 minutes.

Effects

CVS

Methoxamine commonly produces a reflex and intrinsic bradycardia, accompanied by an increase in the systolic and diastolic blood pressures and central venous pressure. The drug has no effect on the cardiac output, but prolongs the effective refractory period and slows atrio-ventricular conduction.

RS

The drug has no effect on respiratory function.

AS

Contraction of gastrointestinal sphincters follows the administration of methoxamine.

GU

The drug produces renal arterial vasoconstriction, leading to a fall in the glomerular filtration rate. Contraction of the pregnant uterus and a decrease in uterine blood flow may occur.

Metabolic/other

Mydriasis, piloerection, and diaphoresis are produced by the drug. Glycogenolysis and gluconeogenesis are stimulated; this is accompanied by a decrease in insulin secretion.

Toxicity/side effects

Headaches, projectile vomiting, sensations of coldness, and the desire to urinate have been reported in association with the use of methoxamine.

Kinetics

There are no data available.

Special points

The drug may precipitate severe hypertension in patients with uncontrolled hyperthyroidism or who are receiving monoamine oxidase inhibitors or tricyclic antidepressants.

Methyldopa

Uses

Methyldopa is used in the treatment of:

1. hypertension and
2. pre-eclampsia.

Chemical

A phenylalanine derivative.

Presentation

As 125/250/500 mg tablets and a suspension containing 50 mg/ml of methyldopa. A solution for intravenous administration containing 50 mg/ml of methyldopa hydrochloride is also available.

Main actions

Antihypertensive.

Mode of action

Methyldopa is metabolized to alpha-methyl noradrenaline which is stored in adrenergic nerve terminals within the central nervous system; the latter is a potent agonist at alpha-2 (pre-synaptic) nerve terminals and reduces central sympathetic discharge, thereby lowering the blood pressure (cf. clonidine).

Routes of administration/doses

The adult oral dose is 0.5–3 g/day in 2–3 divided doses.

Effects

CVS

Methyldopa decreases the systemic vascular resistance with little accompanying change in either cardiac output or heart rate. Postural hypotension occurs uncommonly with the use of the drug.

GU

Methyldopa has little effect on the renal or uteroplacental blood flow, the glomerular filtration rate, or filtration fraction.

Metabolic/other

Plasma renin activity and noradrenaline concentrations decrease after administration of the drug.

Toxicity/side effects

The reported side effects after the administration of methyldopa are legion. Cardiovascular disturbances that may result from the use of the drug include orthostatic hypotension, bradycardia, and peripheral oedema. Central nervous system disturbances may also occur, including sedation, depression, weakness, paraesthesiae, and dizziness. Gastrointestinal, dermatological, and haematological disturbances, including thrombocytopaenia, a positive Coombs's test (in 10–20%), and haemolytic anaemia have also been reported. Methyldopa may also cause hepatic damage.

Kinetics

Absorption

Methyldopa has a variable absorption when administered orally; the bioavailability is 8–62% by this route due to a significant first-pass metabolism.

Distribution

The drug is 50% protein-bound in the plasma; the V_D is 0.21–0.37 l/kg.

Metabolism

Methyldopa is conjugated to sulphate as it traverses the intestinal mucosa and is metabolized in the liver to a variety of poorly characterized metabolites.

Excretion

20–40% of an administered dose is excreted in the urine; two-thirds of this unchanged. The clearance is 2.2–4 ml/min/kg and the elimination half-life is 2.1–2.8 hours.

Special points

The hypotension effects of the drug are additive with those produced by volatile anaesthetic agents; methyldopa also decreases the apparent MAC of the latter.

The action of the drug is prolonged in the presence of renal failure; it is removed by haemodialysis.

Methyldopa commonly produces nasal congestion; care should be exercised during nasal intubation in patients receiving the drug.

Methylphenidate

Uses

Methylphenidate is used for the treatment of:

1. attention deficit hyperactivity disorder (ADHD)
2. narcolepsy and has been used for the treatment of
3. post-anaesthetic shivering
4. hiccuping during general anaesthesia
5. depression and
6. brain injury.

Chemical

A piperidine derivative.

Presentation

As 5/10/20 mg tablets of methylphenidate hydrochloride.

Main actions

Central nervous stimulation.

Mode of action

Methylphenidate binds to the dopamine transporter in pre-synaptic cell membranes, blocking its re-uptake, thereby increasing extracellular dopamine levels. It also affects noradrenaline re-uptake and binds weakly to 5HT receptors.

Routes of administration/doses

The drug is administered orally to a maximum of 60 mg/day in divided doses.

Effects

CVS

The drug causes dose-dependent hypertension and tachycardia.

CNS

Methylphenidate causes generalized CNS stimulation.

Metabolic/other

Methylphenidate decreases growth velocity.

Toxicity/side effects

Insomnia, nervousness, anorexia, hypertension, and tachycardia occur relatively frequently. The drug has significant potential for abuse.

Kinetics

Absorption

Methylphenidate is almost completely absorbed after oral administration.

Distribution

The drug exhibits a low degree of protein binding.

Metabolism

Occurs primarily by de-esterification to ritalinic acid.

Excretion

60–80% of the dose is administered in the urine. The elimination half-life is 2.5 hours.

Metoclopramide

Uses

Metoclopramide is used in the treatment of:

1. digestive disorders, e.g. hiatus hernia, reflux oesophagitis, and gastritis
2. nausea and vomiting due to a variety of causes, e.g. drugs (general anaesthetic agents, opiates, and cytotoxic gents), radiotherapy, hepatic and biliary disorders
3. diagnostic radiology of the gastrointestinal tract
4. migraine and
5. post-operative gastric hypotonia.

Chemical

A chlorinated procainamide derivative.

Presentation

As 10 mg tablets, 15 mg slow-release capsules, a syrup containing 1 mg/ml, and as a clear, colourless solution for injection containing 5 mg/ml of metoclopramide hydrochloride.

Main actions

Increased gastrointestinal motility and antiemetic.

Mode of action

The effects of metoclopramide on gastrointestinal motility appear to be mediated by:

1. antagonism of peripheral dopaminergic (D2) receptors
2. augmentation of peripheral cholinergic responses and
3. a direct action on smooth muscle to increase tone.

The antiemetic effects of the drug appear to be mediated by:

1. central dopaminergic (D2) blockade, leading to an increased threshold for vomiting at the chemoreceptor trigger zone and
2. a decrease in the sensitivity of visceral nerves supplying afferent information to the vomiting centre.

Routes of administration/doses

Metoclopramide may be administered orally, intravenously, or intramuscularly; the adult dose by all routes is 10 mg 8-hourly. A dose of 1–2 mg/kg is recommended for the treatment of nausea and vomiting associated with cisplatin treatment.

Effects

CVS

There have been occasional reports of hypotension during general anaesthesia and cardiac arrest, dysrhythmias, and hypertension in patients with phaeochromocytoma following the administration of metoclopramide.

CNS

Metoclopramide raises the threshold for vomiting at the chemoreceptor trigger zone and prevents apomorphine-induced vomiting in man. The drug has neuroleptic effects (including an antipsychotic action) as would be expected of a centrally acting dopamine antagonist.

AS

Metoclopramide increases the tone of the lower oesophageal sphincter by about 17 mmHg, accelerates gastric emptying and the amplitude of gastric contractions, and accelerates small intestinal transit time. Its effects on large bowel motility are variable. The drug has no effect on gastric secretion.

GU

The drug may increase ureteric peristaltic activity.

Metabolic/other

Metoclopramide stimulates prolactin release and also causes a transient increase in aldosterone secretion.

Toxicity/side effects

Occur in 11% of patients receiving the drug; drowsiness, dizziness, faintness, and bowel disturbances are the most frequently reported side effects. Extrapyramidal side effects occur; the most common manifestations are akathisia and oculogyric crises; extrapyramidal effects occur more frequently with higher doses, in patients with renal impairment, and the elderly. The neuroleptic malignant syndrome has been reported in association with metoclopramide.

Kinetics

Absorption

The drug is rapidly absorbed after oral administration and has a bioavailability by this route of 32–97%. This wide variability is due primarily to first-pass conjugation to sulphate.

Distribution

Metoclopramide is 13–22% protein-bound in the plasma; the V_D is 2.2–3.4 l/kg.

Metabolism

Occurs primarily in the liver; the major metabolite is a sulphate derivative. Two other metabolites have been identified in man.

Excretion

80% of an oral dose is excreted in the urine within 24 hours; 20% of this is unchanged and the remainder appears as non-metabolized drug conjugated to a sulphate or glucuronide and as the sulphated metabolite. The clearance is 8.8–11.6 ml/min/kg and the elimination half-life is 2.6–5 hours.

Metoclopramide is not significantly removed by haemodialysis.

Metronidazole

Uses

Metronidazole is used for:

1. the treatment and prophylaxis of infections due to anaerobic bacteria, especially *Bacteroides fragilis* and *Clostridia* sp., and the treatment of
2. protozoal infections such as amoebiasis, giardiasis, and trichomoniasis
3. acute dental infections and
4. pseudomembranous colitis.

Chemical

A synthetic imidazole derivative.

Presentation

As 200/400/500 mg tablets; 500 mg or 1 g suppositories; and as a clear, colourless 0.5% solution for intravenous injection of metronidazole.

Main actions

Metronidazole is an antimicrobial agent with a high degree of activity against anaerobes and protozoa.

Mode of action

The drug acts via a reactive intermediate which reacts with bacterial DNA so that the resultant DNA complex can no longer function as an effective primer for DNA and RNA polymerases—all nucleic acid synthesis is thus effectively terminated.

Routes of administration/doses

The adult oral dose is 200–800 mg and the corresponding rectal dose is 1 g 8-hourly. The intravenous dose is 500 mg 8-hourly, administered at a rate of 5 ml/min.

Effects

Metabolic/other

Metronidazole decreases the cholesterol content of bile.

Toxicity/side effects

Unpleasant taste, nausea and vomiting, gastrointestinal disturbances, rashes, and darkening of urine have been reported. Peripheral neuropathy and leucopaenia may occur

with chronic use of the drug.

Kinetics

Absorption

The bioavailability of oral metronidazole is 80% and by the rectal route is 75%.

Distribution

Metronidazole is distributed in virtually all tissues and body fluids in concentrations that do not differ markedly from their serum levels. Approximately 10% is protein-bound in the plasma. The V_D is 0.75 l/kg.

Metabolism

Occurs by oxidation and glucuronidation in the liver.

Excretion

60% of the dose is excreted unchanged in the urine; the drug does not usually accumulate in renal failure. The clearance is 1.22 ml/kg/min and the elimination half-life is 6–10 hours.

Special points

Metronidazole increases the anticoagulant effect of warfarin and exhibits a disulfiram-like interaction with alcohol, producing an acute confusional state and vomiting.

Prolongation of the action of vecuronium by the co-administration of the drug has been demonstrated in animals.

Metronidazole may cause reddish brown discoloration of the urine.

Metronidazole is removed by haemodialysis.

Midazolam

Uses

Midazolam is used:

1. for induction of anaesthesia
2. for sedation during endoscopy and procedures performed under local anaesthesia and during intensive care
3. as a hypnotic
4. for premedication prior to general anaesthesia and may be of use
5. in the treatment of chronic pain, including deafferentation syndromes.



Chemical

A water-soluble imidazobenzodiazepine.

Presentation

As a clear, colourless solution of midazolam hydrochloride containing 1/2/5 mg/ml.

Main actions

1. hypnosis
2. sedation
3. anxiolysis
4. anterograde amnesia
5. anticonvulsant and
6. muscular relaxation.

Mode of action

Benzodiazepines are thought to act via specific benzodiazepine receptors found at synapses throughout the central nervous system, but concentrated especially in the cortex and midbrain. Benzodiazepine receptors are closely linked with GABA receptors and appear to facilitate the activity of the latter. Activated GABA receptors open chloride ion channels which then either hyperpolarize or short-circuit the synaptic membrane. Midazolam has kappa-opioid agonist activity *in vitro*, which may explain the mechanism of benzodiazepine-induced spinal analgesia.

Routes of administration/doses

The intramuscular dose (used for premedication) is 0.07–0.08 mg/kg; the intravenous dose for sedation is 0.07–0.1 mg/kg, titrated according to response. The end point for sedation is drowsiness and slurring of speech; response to commands is, however, maintained. The drug may also be administered intrathecally in an adult dose of 0.3–2 mg or epidurally in a dose of 0.1–0.2 mg/kg.

Effects

CVS

Systolic blood pressure decreases by 5% and diastolic pressure by 10% and the systemic vascular resistance falls by 15–33% following the administration of the drug; the heart rate increases by 18%. Midazolam in combination with fentanyl obtunds the pressor response to intubation to a greater extent than thiopental in combination with fentanyl.

RS

Midazolam decreases the tidal volume, but this is offset by an increase in the respiratory rate; the minute volume is thus little changed. Apnoea occurs in 10–77% of patients when midazolam is used as an induction agent. The drug impairs the ventilatory response to hypercapnia.

CNS

The drug produces hypnosis, sedation, and anterograde amnesia. There have been no studies of the anticonvulsant activity of midazolam in man. The cerebral oxygen consumption and cerebral blood flow are decreased in a dose-related manner, but a normal relationship is maintained between the two. When administered intrathecally or epidurally, the drug has antinociceptive effects.

AS

A midazolam–fentanyl induction sequence is associated with a lower incidence of post-operative vomiting than with a thiopental–fentanyl sequence. The drug reduces hepatic blood flow.

GU

Midazolam decreases renal blood flow.

Metabolic/other

Midazolam decreases the adrenergic, but not the cortisol and renin, response to stress. The drug causes significant inhibition of phagocytosis and leucocyte bactericidal activity.

Toxicity/side effects

Side effects are confined to occasional discomfort at the site of injection. Withdrawal phenomena may occur in children after prolonged infusion.

Kinetics

Absorption

The bioavailability when administered by the oral route is 44% and by the intramuscular route is 80–100%.

Distribution

The drug is 96% protein-bound in the plasma; the V_D is 0.8–1.5 l/kg. The V_D may increase to 3.1 l/kg in the critically ill.

Metabolism

Midazolam is virtually completely metabolized in the liver to hydroxylated derivatives which are then conjugated to a glucuronide. Metabolites bind to CNS benzodiazepine receptors and are pharmacologically active.

Excretion

Occurs in the urine, predominantly as the hydroxylated derivatives; renal impairment thus has little effect. The clearance is 5.8–9 ml/min/kg and the elimination half-life is 1.5–3.5 hours. The elimination half-life may increase to 5.4 hours in the critically ill.

Special points

The short duration of action of midazolam is due to its high lipophilicity, high metabolic clearance, and rapid rate of elimination. However, this may not be the case after prolonged dosing on intensive care.

The use of midazolam in premedication decreases the MAC of volatile agents by approximately 15%.

The clinical effects of the drug can be reversed by physostigmine, glycopyrronium bromide, and flumazenil.

Mivacurium

Uses

Mivacurium is used to facilitate intubation and controlled ventilation.

Chemical

A benzylisoquinolinium which is a mixture of three stereoisomers; *trans-trans* (57%), *cis-trans* (36%), *cis-cis* (4–8%). The *cis-cis* isomer is estimated to have less than 5% of the neuromuscular blocking potency of the other two stereoisomers.

Presentation

As a clear, pale yellow, aqueous solution in 5 and 10 ml ampoules containing 2.14 mg/ml of mivacurium hydrochloride. It has a pH of approximately 4.5.

Main action

Competitive, non-depolarizing neuromuscular blockade.

Mode of action

Mivacurium acts by competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction.

Route of administration/doses

Mivacurium is administered by intravenous injection; in adults, the mean dose to reach the ED_{95} is 0.07 mg/kg. The recommended intubating dose in adults is 0.2 mg/kg administered over 30 seconds or a dose of 0.25 mg/kg administered as a divided dose (0.15 mg/kg followed 30 seconds later by 0.1 mg/kg), which provide good to excellent intubating conditions within 2 to 2.5 minutes and 1.5 to 2 minutes (following completion of first divided dose), respectively. Maintenance doses of 0.1 mg/kg are required at approximately 15 minute-intervals in adults and children. Continuous infusion of mivacurium in adults may also be administered at a rate of 8–10 micrograms/kg/min (0.5–0.6 mg/kg/hour). The ED95 in infants and children is 0.07 mg/kg and 0.1 mg/kg, respectively. The corresponding recommended doses for tracheal intubation are 0.15 mg/kg for infants and 0.2 mg/kg for children with times to maximal neuromuscular block of 1.4 and 1.7 minutes, respectively. Average infusion rates to maintain 89–99% neuromuscular block are 11–14 micrograms/kg/min for children aged 2 months to 12 years old (0.7–0.9 mg/kg/hour). Duration of neuromuscular blockade is related to the bolus dose; doses in adults of 0.07, 0.15, 0.2, and 0.25 mg/kg produce clinically effective block for approximately 13, 16, 20, and 25 minutes, respectively. Spontaneous recovery after a continuous infusion is independent of the duration of infusion and is similar to recovery reported for single doses. Tachyphylaxis or cumulative neuromuscular blockade is not associated with continuous infusion of mivacurium. Significant train-of-four fade is not seen during onset of block with mivacurium and intubation of the trachea may be possible before the train-of-four count has been abolished.

Effects

CVS

Mivacurium has minimal cardiovascular effects; a slight (7%) transient decrease in blood pressure and slight (7%) increase in heart rate may occur after rapid intravenous injection. The drug has no significant vagal or ganglion-blocking properties in the normal dosage range.

RS

Neuromuscular blockade leads to apnoea; bronchospasm may occur secondary to histamine release.

Toxicity/side effects

Transient cutaneous flushing occurs in approximately 16% of patients and is the most common side effect. Hypotension, tachycardia, bronchospasm, erythema, and urticaria may all occur with an incidence of less than 1% and are attributed to histamine release. There have been rare reports of fatal anaphylactoid reactions with the administration of mivacurium. Cross-sensitivity may occur with vecuronium, rocuronium, and pancuronium.

Kinetics

Distribution

The V_D of the *trans-trans* isomer is 147 ml/kg, that of the *cis-trans* isomer is 276 ml/kg, and that of the *cis-cis* isomer is 335 ml/kg.

Metabolism

The primary mechanism of metabolism of the *trans-trans* and *cis-trans* stereoisomers is enzymatic hydrolysis by plasma cholinesterases to yield a quaternary alcohol and a quaternary monoester metabolite which appear to be inactive. Some hydrolysis by liver esterases also occurs. The clearance of the *cis-cis* isomer is independent of plasma

cholinesterase.

Excretion

The metabolites are excreted in the bile and urine, together with some unchanged drug. The clearance of the *trans-trans* isomer is 53 ml/kg/min, that of the cis-trans isomer is 99 ml/kg/min, and that of the cis-cis isomer is 4.6 ml/kg/min. The elimination half-life of the trans-trans isomer is 2.0 minutes, that of the cis-trans isomer is 1.8 minutes, and that of the cis-cis isomer is 53 minutes. The clearance of the trans-trans and cis-trans stereoisomers in elderly patients may decrease to 32 and 47 ml/kg/min, respectively, resulting in prolongation of action by approximately 20 to 30%. Renal impairment increases the clinical duration of action of mivacurium by a factor of 1.5 and hepatic impairment increases it by a factor of 3.

Special points

The duration of action of mivacurium is prolonged by isoflurane and enflurane and it is recommended that the initial dose be reduced by 25%. Concomitant use of halothane causes minimal prolongation of action of the drug and dosage reduction is not required. Data suggest that sevoflurane may reduce the mivacurium infusion rate requirement in children by up to 70%. Mivacurium is metabolized by plasma cholinesterase and as such, its duration of activity prolonged in individuals possessing a genetic abnormality of plasma cholinesterase or an acquired reduction in its activity. The following drugs may reduce plasma cholinesterase activity: oral contraceptives, glucocorticoids, monoamine oxidase inhibitors, ketamine, lithium, ester local anaesthetic agents, metoclopramide, ecothiopate, trimetaphan, and edrophonium. Acquired conditions associated with reduced activity of plasma cholinesterase include: malignancy, renal impairment, hepatic impairment, cardiac failure, pregnancy, thyrotoxicosis. The following drugs enhance the neuromuscular effects of mivacurium: aminoglycoside antibiotics, propranolol, calcium channel blockers, diuretics, and magnesium and lithium salts.

In patients who are obese, the ideal body weight should be used for dose calculation.

Mivacurium can be reversed using neostigmine (together with an inhibitor of vagal activity). Administration of between 0.03–0.06 mg/kg of neostigmine at 10% recovery from neuromuscular block produces 95% recovery of muscle twitch response and a T4:T1 ratio of >75% in approximately 10 minutes.

Mivacurium does not act as a trigger agent for malignant hyperpyrexia in animal models.

The drug is physically incompatible with alkaline solutions (e.g. barbiturates).

Morphine

Uses

Morphine is used:

1. for premedication
2. as an analgesic in the management of moderate to severe pain
3. in the treatment of left ventricular failure
4. to provide analgesia during terminal care and
5. in combination with kaolin in the symptomatic treatment of diarrhoea.



Chemical

A phenanthrene derivative.

Presentation

As 5/10/30/60/100/200 mg tablets, a syrup containing 2/10/20 mg/ml, as 15/30 mg suppositories, and as a clear, colourless solution for injection containing 10/15/30 mg/ml of morphine sulphate; preservative-free morphine must be used for epidural/spinal use.

Main actions

Analgesia and respiratory depression.

Mode of action

Morphine is an agonist at mu- and kappa-opioid receptors. Opioids appear to exert their effects by increasing intracellular calcium concentration which in turn increases potassium conductance and hyperpolarization of excitable cell membranes. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routes of administration/doses

The initial adult oral dose is 5–20 mg 4-hourly, increased as required. The dose by the rectal route is 15–30 mg 4-hourly. The corresponding intramuscular or subcutaneous dose is 0.1–0.2 mg/kg and the intravenous dose is 0.05–0.1 mg/kg 3–4-hourly. Morphine may also be administered intrathecally; an adult dose of 0.2–1 mg has been recommended. The drug has a peak analgesic effect 30–60 minutes after intramuscular injection and has duration of effect of 3–4 hours.

Effects

CVS

Morphine has minimal effects on the cardiovascular system; the predominant effect is that of orthostatic hypotension secondary to a decrease in the systemic vascular resistance, at least part of which is mediated by histamine release. The drug may also cause bradycardia when administered in high doses.

RS

The principal effect of the drug is respiratory depression with a decreased ventilatory response to hypoxia and hypercapnia. Morphine also has a potent antitussive action. Bronchoconstriction may occur with the use of high doses of the drug.

CNS

Morphine is a potent analgesic agent and may also cause drowsiness, relief of anxiety, and euphoria. Miosis is produced by the drug as a result of stimulation of the Edinger–Westphal nucleus. Seizures and muscular rigidity may occur with the use of high doses of morphine.

AS

Morphine decreases gastrointestinal motility and decreases gastric acid, biliary, and pancreatic secretions; it also increases the common bile duct pressure by causing spasm of the sphincter of Oddi. The drug may also cause nausea, vomiting, and constipation.

GU

The drug increases the tone of the ureters, bladder detrusor muscle, and sphincter, and may precipitate urinary retention.

Metabolic/other

Mild diaphoresis and pruritus may result from histamine release. Morphine increases the secretion of ADH and may, therefore, lead to impaired water excretion and hyponatraemia. The drug causes a transient decrease in adrenal steroid secretion.

Toxicity/side effects

Respiratory depression, nausea and vomiting, hallucinations, and dependence may complicate the use of morphine. Pruritus may occur after epidural or spinal administration of the drug.

Kinetics

Absorption

Morphine is well absorbed when administered orally; the bioavailability by this route is 15–50% due to an extensive first-pass metabolism.

Distribution

The drug is 20–40% protein-bound in the plasma, predominantly to albumin; the VD is 3.4–4.7 l/kg. Morphine equilibrates slowly between the plasma and CSF; there is no clear correlation between the degree of analgesia and the plasma concentration of the drug.

Metabolism

Occurs in the liver to morphine-3-glucuronide, morphine- 6-glucuronide, and normorphine. In animal models, morphine-6-glucuronide has analgesic effects and morphine-3-glucuronide has effects on arousal. Enterohepatic cycling of the metabolites probably does not occur.

Excretion

Occurs predominantly in the urine as the glucuronide conjugates; 7–10% appears in the faeces as conjugated morphine. The clearance is 12–23 ml/min/kg and the elimination half-life is 1.7–4.5 hours. Cumulation of morphine-6-glucuronide occurs in the presence of renal failure; a reduction in the dose of the drug is necessary under these circumstances.

Special points

Morphine should be used with caution in the presence of hepatic failure as the drug may precipitate encephalopathy. Similarly, the use of the drug in patients with hypopituitarism may precipitate coma. In common with other opioids, morphine decreases the apparent MAC of co-administered volatile agents. The actions of the drug are all reversed by naloxone, although the analgesia afforded by the epidural administration of morphine is well preserved after the administration of naloxone.

Morphine is not removed by haemodialysis or by peritoneal dialysis.







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Nalbuphine

Uses

Nalbuphine is used:

1. for premedication and
2. as an analgesic in the treatment of moderate to severe pain.

Chemical

A semi-synthetic phenanthrene derivative.

Presentation

As a clear, colourless solution for injection containing 10 mg/ml of nalbuphine hydrochloride.

Main action

Analgesia.

Mode of action

Nalbuphine is an agonist at kappa-opioid receptors and an antagonist at mu-opioid receptors; it thus produces analgesia (a kappa effect) whilst antagonizing both the respiratory depressant effects and the potential for dependency that are associated with the mu-receptor.

Routes of administration/doses

The drug may be administered intravenously, intramuscularly, or subcutaneously in an adult dose of 10–20 mg. Nalbuphine acts within 2–3 minutes when administered intravenously and within 15 minutes when administered intramuscularly. The duration of action is 3–6 hours.

Effects

CVS

Nalbuphine has little significant effect on the heart rate, mean arterial pressure, systemic or pulmonary vascular resistance, or cardiac output.

RS

The drug has a respiratory depressant effect equal to that of morphine, but demonstrates a ceiling effect at a dose of 0.5 mg/kg. It will antagonize the respiratory depressant effects of co-administered pure mu-agonists whilst adding to the analgesic effect of the latter.

CNS

Nalbuphine has an analgesic potency equivalent to that of morphine. It has no euphoriant effects.

AS

The drug causes less inhibition of gastrointestinal activity than other opioids.

Toxicity/side effects

Sedation, dizziness, vertigo, dry mouth, and headache may complicate the use of nalbuphine. The drug causes less nausea and vomiting, psychotomimetic effects, and dependence than does morphine.

Kinetics

Absorption

The bioavailability by the oral route is 12–17% due to a significant first-pass hepatic metabolism. The bioavailability is 80% by the intramuscular and subcutaneous routes.

Distribution

Nalbuphine is 25–40% protein-bound in the plasma; the V_D is 162–498 l.

Metabolism

Occurs predominantly in the liver to two inactive conjugates which are secreted into the bile.

Excretion

The metabolites are predominantly excreted (with some unchanged nalbuphine) via the faeces. A small fraction is excreted unchanged in the urine. The clearance is 0.8–2.3 l/min and the elimination half-life is 110–160 minutes. Care should be exercised during the use of the drug in patients with renal or hepatic impairment.

Special points

Nalbuphine is ineffective in obtunding the cardiovascular responses to laryngoscopy and intubation. The drug will precipitate withdrawal symptoms in opiate addicts; its effects are reversed by

naloxone.

Nalbuphine has been used in the management of post-operative shivering.

Naloxone

Uses

Naloxone is used for:

1. the reversal of respiratory depression due to opioids
2. the diagnosis of suspected opioid overdose and has been used in the treatment of
3. clonidine overdose.

Chemical

A substituted oxymorphone derivative.

Presentation

As a clear solution for injection containing 0.02/0.4 mg/ml of naloxone hydrochloride.

Main actions

Reversal of mu-opioid receptor effects such as sedation, hypotension, respiratory depression, and the dysphoric effects of partial agonists. The drug will precipitate acute withdrawal symptoms in opiate addicts.

Mode of action

Naloxone is a competitive antagonist at mu-, delta-, kappa-, and sigma-opioid receptors.

Routes of administration/doses

For the reversal of opioid-induced respiratory depression, the drug should be administered intravenously in small incremental doses until the desired end point of reversal of respiratory depression without reversal of analgesia is reached; in adults, 0.1–0.2 mg will normally achieve this effect. In the treatment of known or suspected opioid overdose, 0.4–2.0 mg may be administered intravenously, intramuscularly, or subcutaneously. The drug acts within 2 minutes when administered intravenously and has duration of effect (approximately 20 minutes) that may be shorter than the opioid whose effects it is desired to counteract. It may therefore be necessary to administer additional doses of naloxone intravenously or intramuscularly.

Effects

CVS

The drug has no effect at normal doses. In doses of 0.3 mg/kg, the blood pressure may increase. Naloxone has been shown to reverse the hypotension associated with endotoxic and hypovolaemic shock in some animal studies.

CNS

Naloxone causes slight drowsiness at very high doses. Some forms of stress-induced analgesia are obtunded by naloxone; the drug also decreases the tolerance to pain in subjects with high pain thresholds.

AS

Naloxone reverses opioid-induced spasm of the sphincter of Oddi.

Toxicity/side effects

Serious ventricular dysrhythmias occurring in patients with irritable myocardia after the administration of naloxone have been reported.

Kinetics

Absorption

The drug is 91% absorbed when administered orally, but has a bioavailability by this route of 2% due to an extensive first-pass metabolism.

Distribution

The drug is 46% protein-bound in adult plasma. The V_D is 2 l/kg.

Metabolism

The drug is metabolized in the liver, primarily by conjugation to glucuronide.

Excretion

The clearance is 25 ml/min/kg and the plasma half-life is 1.2 hours.

Special points

Naloxone is effective in alleviating the pruritus, nausea, and respiratory depression associated with the epidural or spinal administration of opioids.

Neostigmine

Uses

Neostigmine is used:

1. for the reversal of non-depolarizing neuromuscular blockade and in the treatment of
2. myasthenia gravis
3. paralytic ileus and
4. urinary retention.

Chemical

A quaternary amine which is an ester of an alkyl carbamic acid.

Presentation

As 15 mg tables of neostigmine bromide and as a clear, colourless solution for injection containing 2.5 mg/ml of neostigmine metilsulfate. A fixed dose combination containing 0.5 mg of glycopyrronium bromide and 2.5 mg of neostigmine metilsulfate per ml is also available.

Main actions

Cholinergic.

Mode of action

Neostigmine is a reversible, acid-transferring cholinesterase inhibitor which binds to the esteratic site of acetylcholinesterase and is hydrolyzed by the latter, but at a much slower rate than is acetylcholine. The accumulation of acetylcholine at the neuromuscular junction allows the competitive antagonism of any non-depolarizing relaxant that may be present.

Routes of administration/doses

The adult oral dose is 15–50 mg 2–4-hourly. The intravenous dose for the reversal of non-depolarizing neuromuscular blockade is 0.05–0.07 mg/kg, administered slowly and in combination with an appropriate dose of an anticholinergic agent. The peak effect of the drug when administered intravenously occurs at 7–11 minutes; a single dose of neostigmine has duration of action of 40–60 minutes.

Effects

CVS

The effects of neostigmine on the cardiovascular system are variable and depend upon the prevailing autonomic tone. The drug may cause bradycardia, leading to a fall in cardiac output; it decreases the effective refractory period of cardiac muscle and increases conduction time in conducting tissue. In high doses, neostigmine may cause hypotension secondary to a central effect.

RS

Neostigmine increases bronchial secretion and may cause bronchoconstriction.

CNS

In small doses, the drug has a direct action on skeletal muscle, leading to muscular contraction. In high doses, neostigmine may block neuromuscular transmission by the combination of a direct effect and by allowing the accumulation of acetylcholine. Miosis and failure of accommodation may be precipitated by the administration of the drug.

AS

The drug increases salivation, lower oesophageal and gastric tone, gastric acid output, and lower gastrointestinal tract motility. Nausea and vomiting may occur.

GU

Neostigmine increases ureteric peristalsis and may lead to involuntary micturition.

Metabolic/other

Sweating and lachrymation are increased.

Toxicity/side effects

The side effects are manifestations of its pharmacological actions as described above. Cardiac arrest has been reported after the use of neostigmine.

Kinetics

Data are incomplete.

Absorption

Neostigmine is poorly absorbed when administered orally; the bioavailability by this route is 1–2%.

Distribution

The drug is highly ionized and, therefore, does not cross the blood–brain barrier to any significant extent. Neostigmine is 6–10% protein-bound in the plasma; the V_D is 0.4–1 l/kg.

Metabolism

Neostigmine is predominantly metabolized by plasma esterases to a quaternary alcohol; some hepatic metabolism with subsequent biliary excretion may also occur.

Excretion

50–67% of an administered dose is excreted in the urine.

The clearance is 5.7–11.1 ml/min/kg and the elimination half-life is 15–80 minutes; the clearance is decreased and the elimination half-life is increased in the presence of renal impairment.

Special points

Neostigmine prolongs the duration of action of suxamethonium. There is some evidence that the use of neostigmine to reverse neuromuscular blockade is associated with an increased incidence of gastrointestinal anastomotic breakdown.

Nifedipine

Uses

Nifedipine is used in the treatment of:

1. angina
2. mild to severe hypertension (including pregnancy-induced hypertension)
3. Raynaud's phenomenon and
4. coronary artery spasm occurring during coronary angiography or angioplasty.

Chemical

A dihydropyridine derivative.

Presentation

As 5/10 mg capsules and a slow-release preparation containing 10/20/30/60 mg per tablet. A fixed dose combination with atenolol is also available.

Main actions

Relaxation of arterial smooth muscle in both the coronary and peripheral circulations.

Mode of action

Nifedipine causes competitive blockade of cell membrane slow calcium channels, leading to decreased influx of calcium ions into cells. This produces electromechanical decoupling, inhibition of contraction, and relaxation of cardiac and smooth muscle fibres and leads to a negative inotropic effect and vasodilatation. It may also act by increasing red cell deformability and preventing platelet clumping and thromboxane release.

Routes of administration/doses

The adult oral dose of nifedipine is 10–20 mg 8-hourly (20–40 mg 12-hourly for the slow-release preparation), 100–200 micrograms may be infused via a coronary catheter over 2 minutes.

Effects

CVS

The mean arterial pressure decreases by 20–33%; this effect is more pronounced in hypertensive patients. This is accompanied by a reflex increase in heart rate by up to 28%. The systemic and pulmonary vascular resistance and left ventricular end-diastolic and pulmonary artery pressures all decrease. Cardiac output is increased; nifedipine also causes a sustained relaxation of epicardial conductance vessels, leading to increased coronary blood flow in patients with ischaemic heart disease. Nifedipine is 3–10 times more effective in inhibiting contraction in coronary artery smooth muscle than in myocardial contractile cells. The drug may also protect the myocardium during reperfusion after cardiac bypass.

RS

Nifedipine demonstrates no intrinsic bronchodilator effect in most studies. The drug appears to inhibit hypoxic pulmonary vasoconstriction.

CNS

The drug causes a marginal increase in the cerebral blood flow due to vasodilatation of large cerebral vessels.

AS

Contractility throughout the gut and lower oesophageal pressure are decreased by nifedipine. The hepatic blood flow is increased.

GU

Nifedipine has no marked effect on the renal blood flow or glomerular filtration rate. Uterine activity is decreased by the drug.

Metabolic/other

Plasma renin activity and catecholamines are increased; short-term use may decrease glucose tolerance. Platelet aggregation is impaired by the drug; thromboxane synthesis is inhibited and nifedipine may thus decrease thromboxane-induced coronary artery spasm.

Toxicity/side effects

Occur in 20% of patients; headache, flushing, and dizziness (secondary to vasodilatation) are common; oedema of the legs, eye pain, and gum hyperplasia have been reported.

Kinetics

Absorption

Nifedipine is completely absorbed when administered orally; the bioavailability by this route is 45–68%.

Distribution

The drug is 92–98% protein-bound in the plasma, the V_D is 0.62–1.12 l/kg.

Metabolism

95% of the dose is metabolized in the liver to three inactive metabolites.

Excretion

90% of the metabolites are excreted in the urine, the rest in the faeces. The clearance is 27–66 l/hour and the elimination half-life is 1.3–11 hours, dependent upon the route of administration.

Special points

Nifedipine is a safe and effective drug for the treatment of post-surgical hypertension; the reduction in mean arterial pressure is associated with an increase in cardiac index and systemic oxygen

transport.

All volatile agents in current use decrease calcium ion release from the sarcoplasmic reticulum and decrease calcium ion flux into cardiac cells; the negatively inotropic effects of nifedipine are thus additive with those of the volatile agents. When used in combination with isoflurane, the negative inotropic effects of the drugs are additive and may result in a profound decrease in cardiac output.

Experiments in animals have demonstrated an increased risk of sinus arrest if volatile agents and calcium antagonists are used concurrently. If withdrawn acutely (especially in the post-operative period) after chronic oral use, severe rebound hypertension may result.

Calcium channel antagonists may also:

1. reduce the MAC of volatile agents by up to 20% and
2. increase the efficacy of neuromuscular blocking agents.

Administration of nifedipine immediately prior to induction appears to aggravate redistribution hypothermia. The drug is not removed by dialysis.

Nimodipine

Uses

Nimodipine is used:

1. in the prevention and treatment of cerebral vasospasm secondary to subarachnoid haemorrhage and may be of use in the management of
2. migraine

3. acute cerebrovascular accidents and
4. drug-resistant epilepsy.

Chemical

A dihydropyridine.

Presentation

As an intravenous infusion containing 200 micrograms/ml of nimodipine containing ethanol 20% and macrogol '400' 17%, and as 30 mg tablets.

Main action

Dilation of cerebral vessels, leading to improved cerebral perfusion.

Mode of action

Nimodipine is a calcium antagonist that binds to specific sites in the cell membranes of vascular smooth muscle and prevents calcium ion influx through 'slow' calcium ion channels, leading to vasodilatation; the drug has a relatively specific action on cerebral arterioles.

Routes of administration/doses

The drug should be administered into a running crystalloid infusion via a central vein at the rate of 1 mg/hour for the first 2 hours and thereafter at the rate of 2 mg/hour for 5–14 days. The oral dose is 60 mg every 4 hours starting within 4 days of subarachnoid haemorrhage.

Effects

CVS

In normal subjects, doses of 2 mg/hour decrease the systolic and diastolic blood pressure. In the anaesthetized patient, an infusion of 1 micrograms/kg/min decreases the systemic vascular resistance by 10–40% and increases cardiac output by 25–45%.

CNS

Nimodipine increases the cerebral blood flow by up to 18% with no demonstrable 'steal' effect in patients who have had a subarachnoid haemorrhage. The use of nimodipine in such patients leads to a significant reduction in mortality and morbidity.

Toxicity/side effects

Side effects occur infrequently although flushing, headache, nausea, hypotension, and reversible abnormalities of liver function tests may complicate the use of the drug.

Kinetics

Absorption

Nimodipine is rapidly and well absorbed when administered orally, but has a bioavailability by this route of only 3–28% due to a significant first-pass metabolism.

Distribution

The drug is 98% protein-bound in the plasma; the V_D is 0.94–2.3 l/kg.

Metabolism

Nimodipine is initially demethylated and dehydrogenated to an inactive pyridine analogue which subsequently undergoes further degradation.

Excretion

Half of the dose appears as metabolites in the urine and a third in the faeces. The clearance is 420–520 l/hour and the elimination half-life is 0.9–7.2 hours (dependent upon the route of administration). The clearance is decreased by hepatic impairment; the effect of renal impairment is unclear.

Special points

Nimodipine has some effect in obtunding the cardiovascular responses to intubation and surgical stimulation; the peak blood pressures post-intubation and post-incision are consistently 10–15% lower in patients receiving the drug than those recorded in untreated patients.

The drug is adsorbed onto polyvinyl chloride tubing and is also light-sensitive; however, it remains stable in diffuse daylight for up to 10 hours.

Nitric oxide

Uses

Nitric oxide (NO) is used as a selective pulmonary vasodilator in pulmonary hypertension.

Chemical

An inorganic gas.

Presentation

In aluminium cylinders containing 100/800 ppm nitric oxide and nitrogen; the cylinders may contain either 353 l at standard temperature and pressure (STP) of nitric oxide in nitrogen or 1963 l at STP. Pure nitric oxide is toxic and corrosive. Nitric oxide can also be supplied via stainless steel medical gas piping.

Main actions

Vasodilatation.

Mode of action

Nitric oxide is produced *in vivo* by NO synthase which uses the substrate L-arginine. Nitric oxide diffuses to the vascular smooth muscle layer and stimulates guanylate cyclase; the cGMP produced activates a phosphorylation cascade which leads to smooth muscle relaxation and vasodilatation.

Route of administration/doses

Nitric oxide is administered by inhalation in a dose of 5–20 ppm; the drug can either be injected into the patient limb of the inspiratory circuit of a ventilator during inspiration only or administered using a continuous flow system which delivers nitric oxide throughout the respiratory cycle. The former technique reduces a 'bolus' effect seen with a continuous flow technique in addition to reducing nitrogen dioxide formation. This latter effect is achieved by decreasing the time allowed for oxygen and nitric oxide to mix. The delivery system is designed to minimize the oxidation of nitric oxide to nitrogen dioxide. Monitoring of nitric oxide concentrations can be achieved by a chemiluminescent monitor or electrochemical detector.

Effects

CVS

Nitric oxide is a potent vasodilator that mediates the hypotension and significant vascular leak characteristic of septic shock. Inhaled nitric oxide is a selective pulmonary vasodilator since it is avidly bound to haemoglobin and thereby inactivated before reaching the systemic circulation. Nitric oxide released from vascular endothelium inhibits platelet aggregation and attenuates platelet and white cell adhesion.

RS

Nitric oxide inhibits hypoxic pulmonary vasoconstriction and preferentially increases blood flow through well-ventilated areas of the lung, thereby improving ventilation:perfusion relationships.

CNS

Nitric oxide increases cerebral blood flow and appears to have physiological role as a neurotransmitter within the autonomic and central nervous systems.

GU

Nitric oxide may play a role in the regulation of renin production and sodium homeostasis in the kidney. It is the physiological mediator of penile erection.

Metabolic/other

Nitric oxide released from macrophages reacts with superoxide ion to form the free radical peroxynitrite which is toxic to bacteria. Insulin release appears to be modulated by nitric oxide.

Toxicity/side effects

Exposure to 500–2000 ppm of nitric oxide results in methaemoglobinaemia and pulmonary oedema. Contamination by nitrogen dioxide can similarly lead to pneumonitis and pulmonary oedema.

Kinetics

Absorption

Nitric oxide is highly lipid-soluble and diffuses freely across cell membranes.

Metabolism

Following inhalation, nitric oxide combines with oxyhaemoglobin that is 60–100% saturated, producing methaemoglobin and nitrate. Nitric oxide has a half-life of <5 seconds. During the first 8 hours of nitric oxide exposure, methaemoglobin concentrations increase.

Excretion

The main metabolite is nitrate (70%) which is excreted by the kidneys.

Special points

Prolonged inhalation (up to 27 days) of the gas appears safe and is not associated with tachyphylaxis.

Abrupt cessation of nitric oxide can cause a profound decrease in PaO_2 and increase in pulmonary artery pressure, possibly via down-regulation of endogenous NO production or guanylate cyclase activity. The dose should be reduced slowly to avoid this from occurring even in patients who may not have clinically responded to nitric oxide therapy. During treatment, concentrations of nitrogen dioxide must be monitored.

Nitric oxide therapy is contraindicated in neonates known to have circulations dependent on a right-to-left shunt or significant left-to-right shunts.

Development of methaemoglobinaemia usually rapidly resolves on discontinuation of treatment over several hours. Persistent methaemoglobinaemia can be treated using methylene blue.

Mortality does not appear to be affected by the administration of NO in ARDS.

The Occupational Exposure Limits are 25 ppm for nitric oxide and 3 ppm for nitrogen dioxide.

Nitrous oxide

Uses

Nitrous oxide is used:

1. as an adjuvant to the induction and maintenance of general anaesthesia
2. as an analgesic during labour and other painful procedures
3. in cryosurgery as a refrigerant.

Chemical

An inorganic gas.

Presentation

As a liquid in cylinders at a pressure of 44 bar at 15°C; the cylinders are French blue and are available in six sizes (C–J, containing 450–18 000 l, respectively), following manufacture by heating ammonium nitrate to 250°C. The gauge pressure does not correlate with cylinder content until all N2O is in the gaseous phase. It is a sweet-smelling, colourless gas; it is non-flammable, but supports combustion. It has a molecular weight of 44, specific gravity of the gas of 1.53, a boiling point of –88.5°C, a critical temperature of 36.5°C, and a critical pressure of 71.7 atmospheres. Due to the critical temperature being close to ambient temperature, the filling ratio of the cylinder is 0.75 in temperate regions, but reduced to 0.67 in tropical regions. The MAC of nitrous oxide is 105, the oil:water partition coefficient 3.2, and the blood:gas partition coefficient is 0.47 (compared to 0.015 for nitrogen). There are trace amounts of carbon dioxide, carbon monoxide, and nitric oxide/nitrogen dioxide present in cylinders of nitrous oxide at the following maximum amounts: 300 vpm, 10 vpm, 2 vpm, respectively.

Entonox is the trade name given to a 50/50 mixture of oxygen and nitrous oxide and is produced by bubbling oxygen through liquid nitrous oxide. It is available in cylinders which are French blue with white and blue shoulders in the following four sizes: SD, D, F, G containing 440–5000 l, respectively. The cylinder pressure is 137 bar at 15°C. At normal temperatures, both of the components of Entonox are present in pressurized cylinders in the gaseous phase (due to the Poynting effect); below its pseudocritical temperature of –7°C, liquefaction of nitrous oxide occurs, resulting in separation of the two components.

Main actions

Analgesia and depression of the central nervous system

Mode of action

The mode of action of the anaesthetic action of nitrous oxide is predominantly via non-competitive inhibition of the NMDA subtype of glutamate receptors. It may also act via the two pore domain potassium channels (e.g. TREK-1) which increase potassium conductance and subsequent neurone hyperpolarization. It appears to have minimal effect at GABA type A receptors. The analgesic action of nitrous oxide occurs via supraspinal activation of opiodergic neurones and GABA-ergic interneurons in the periaqueductal grey matter and noradrenergic neurones in the locus ceruleus. The latter activation pathway appears to be triggered by hypothalamic release of corticotrophin-releasing factor, mediated by nitrous oxide antagonism at the NMDA receptor.

Route of administration/doses

Nitrous oxide is administered by inhalation; a concentration of 70% in oxygen is conventionally used as an adjunct to general anaesthesia. Entonox is used to provide analgesia for a range of painful procedures.

Effects

CVS

Nitrous oxide decreases myocardial contractility *in vitro*; *in vivo*, the mean arterial pressure is usually well maintained by a reflex increase in peripheral vascular resistance. Deterioration in left ventricular function occurs when nitrous oxide is added to a high-dose opioid oxygen anaesthetic sequence, volatile agents, or a propofol infusion.

RS

The gas causes a slight depression in respiration with a decrease in tidal volume and increase in respiratory rate. Nitrous oxide is non-irritant and does not cause bronchospasm.

CNS

Nitrous oxide is a central nervous system depressant and, when administered in a concentration of 80%, will cause loss of consciousness in most subjects. The gas is a powerful analgesic in concentrations >20%. Its administration causes a rise in intracranial pressure.

GU

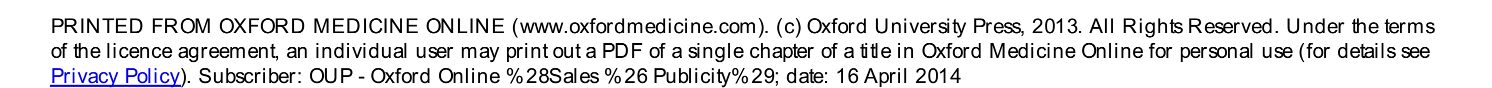
Nitrous oxide has no effect on uterine tone.

Toxicity/side effects

15% of patients receiving nitrous oxide will experience nausea and vomiting. The gas is 35 times more soluble than nitrogen in the blood; nitrous oxide will, therefore, cause an increase in the size of air-filled spaces (e.g. pneumothorax, intestines, air cysts in the middle ear) in the body. A further manifestation of this physical property of the gas is the Fink Effect (diffusion hypoxia); when nitrous oxide is discontinued, the ingress of the gas into the alveoli lowers the alveolar oxygen concentration. The prolonged use of high concentrations of nitrous oxide (>6 hours) leads to inactivation via oxidation of the cobalt ion of the cobalamin (vitamin B12) form. The resulting cobalt cation prevents cobalamin from acting as a coenzyme for methionine synthetase. The latter cytosolic enzyme is involved in the synthesis of DNA, RNA, myelin, and catecholamines. The resultant clinical syndrome is akin to pernicious anaemia, megaloblastic anaemia, and pancytopaenia. 20% of elderly patients are deficient in cobalamin. Nitrous oxide may decrease proliferation of human peripheral blood mononuclear cells and alter neutrophil chemotaxis. Prolonged use/abuse of the gas may lead to altered mental state, paraesthesiae, ataxia, lower limb weakness, and spasticity. Subacute combined degeneration of the cord may occur. In neonatal rats, nitrous oxide exacerbates isoflurane-induced apoptotic neuronal death. Nitrous oxide is teratogenic in animals when administered during early pregnancy. The maximum exposure in the UK to nitrous oxide is 100 ppm.

Kinetics

Absorption



Nitrous oxide diffuses freely across the normal alveolar epithelium. The rate of uptake of the gas is increased by a decreased cardiac output, an increased concentration, and by increased alveolar ventilation.

Due to its relative insolubility, alveolar concentration of the gas approaches the inspired concentration rapidly; 90% equilibration within 15 minutes and 100% equilibration within 5 hours.

Metabolism

Little, if any, metabolism occurs in man.

Excretion

Nitrous oxide is excreted unchanged through the lungs and skin.

Special points

Nitrous oxide exhibits the following two effects. The 'concentration effect' implies that the greater inspired anaesthetic concentration, the more rapid the rise in alveolar concentration. The 'second gas effect' refers to the ability of one gas administered in a high concentration (e.g. nitrous oxide) to accelerate the uptake of another gas (e.g. halothane) that is co-administered. 66% nitrous oxide in oxygen decreases the MAC of halothane to 0.29, of enflurane to 0.6, of isoflurane to 0.5, of sevoflurane to 0.66, and of desflurane to 2.8. The use of nitrous oxide is safe in patients susceptible to malignant hyperpyrexia.

Noradrenaline

Uses

Noradrenaline is used in the treatment of refractory hypotension.

Chemical

A catecholamine.

Presentation

As a clear, colourless solution containing 2 mg/ml of noradrenaline bitartrate for dilution prior to infusion.

Main action

Increased systemic vascular resistance.

Mode of action

Noradrenaline is a directly and indirectly acting sympathomimetic amine that exerts its action predominantly at alpha-adrenergic receptors, with a minor action at beta-receptors.

Routes of administration/doses

Noradrenaline is administered through a central vein as an infusion in glucose or saline in a concentration of 4 micrograms/ml at a rate titrated according to the response desired. The drug has duration of action of 30–40 minutes; tachyphylaxis occurs with prolonged administration.

Effects

CVS

Noradrenaline increases the peripheral vascular resistance, leading to an increase in the systolic and diastolic blood pressure; the cardiac output remains unchanged or decreases slightly. Reflex vagal stimulation leads to a compensatory bradycardia. The drug produces coronary vasodilatation, leading to a marked increase in coronary blood flow. The circulating blood volume is reduced by noradrenaline due to loss of protein-free fluid to the extracellular fluid. Noradrenaline may also cause nodal rhythm, atrio-ventricular dissociation, and ventricular dysrhythmias.

RS

The drug causes a slight increase in the minute volume accompanied by a degree of bronchodilatation.

CNS

The cerebral blood flow and oxygen consumption are decreased by the administration of noradrenaline; mydriasis also occurs.

AS

The hepatic and splanchnic blood flow are decreased by the drug.

GU

Noradrenaline decreases the renal blood flow; the glomerular filtration rate is usually well maintained. The tone of the bladder neck is increased. Noradrenaline increases the contractility of the pregnant uterus; this may lead to fetal bradycardia and asphyxia.

Metabolic/other

Noradrenaline may decrease insulin secretion, leading to hyperglycaemia; the concentration of free fatty acids and the plasma renin activity may increase.

Toxicity/side effects

Anxiety, headache, photophobia, pallor, sweating, gangrene, and chest pain may occur with the use of the drug. Extravasation of noradrenaline may lead to sloughing and

tissue necrosis.

Kinetics

Absorption

Noradrenaline undergoes significant first-pass metabolism and is inactive when administered orally.

Distribution

The V_D is 0.09–0.4 l/kg.

Metabolism

Exogenous noradrenaline is metabolized by two pathways; by oxidative deamination to the aldehyde by mitochondrial monoamine oxidase (in liver, brain, and kidney) and by methylation by cytoplasmic catechol-O-methyl transferase to normetanephrine. The predominant metabolite appearing in the urine is 3-methoxy, 4-hydroxymandelic acid (VMA).

Excretion

5% of an administered dose of noradrenaline is excreted unchanged; the clearance is 27.9–100 ml/min/kg and the half-life is 0.57–2.4 minutes.

Special points

The use of noradrenaline during halothane anaesthesia may lead to the appearance of serious cardiac dysrhythmias; if co- administered with MAOIs or tricyclic antidepressants, serious hypertensive episodes may be precipitated.

The drug is pharmaceutically incompatible with barbiturates and sodium bicarbonate.







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Omeprazole

Uses

Omeprazole is used in the treatment of:

1. peptic ulcer disease
2. peptic oesophagitis
3. the Zollinger–Ellison syndrome
4. prevention of NSAID-associated ulcers and
5. following endoscopic treatment of peptic ulcer bleeding.

Chemical

A substituted benzimidazole derivative.

Presentation

As capsules containing 10/20/40 mg of omeprazole and in 40 mg vials as a powder of the sodium salt of omeprazole.

Main actions

Inhibition of basal and stimulated gastric acid secretion.

Mode of action

Omeprazole acts via a derivative which binds irreversibly to parietal cell H-K-ATPase and non-competitively inhibits it. The activity of the parietal cell 'proton pump', which represents the final common pathway of hydrogen ion secretion, is thus inhibited.

Routes of administration/doses

The adult oral dose for the treatment of peptic ulcer disease is 20–40 mg daily for a period of 4–8 weeks; the corresponding dose for the treatment of the Zollinger–Ellison syndrome is 20–120 mg daily. The intravenous dose is administered over 5 minutes.

Effects

AS

Omeprazole significantly reduces the volume of gastric juice, but has no effect on the rate of gastric emptying. A single 20 mg dose will effectively control acid secretion for 24 hours. In animals, orally administered omeprazole appears to confer protection against stress-induced gastric ulceration.

Metabolic/Other

The drug has no demonstrable effect on endocrine function.

Toxicity/side effects

Omeprazole is usually well tolerated; rashes, nausea, headache, gastrointestinal disturbances, liver dysfunction, and arrhythmia may occur.



Kinetics

Absorption

Oral omeprazole is rapidly absorbed and has a bioavailability of 40–97%, dependent upon the formulation and dose. The drug may increase its own bioavailability since degradation occurs under acidic conditions.

Distribution

The drug is 95–96% protein-bound in the plasma, predominantly to albumin and alpha-1-acid glycoprotein. The V_D is 0.3–0.4 l/kg.

Metabolism

Omperazole is rapidly and completely metabolized by oxidation to a sulphone, reduction to a sulphide, and by hydroxylation.

Excretion

80% of an oral dose is excreted in the urine, the remainder in the faeces. The clearance is 533–666 ml/min and the elimination half-life is 0.5–1.5 hours.

Special points

Omeprazole is 2–10 times as potent as cimetidine; furthermore, it heals ulcers significantly more rapidly than conventional H_2-antagonist regimes and may be effective in patients resistant to conventional therapy. Proton pump inhibitors reduce the risk of rebleeding from peptic ulcer disease and the need for surgery

The pharmacokinetics of the drug are unaltered by renal impairment and it is not removed by haemodialysis; no dose reduction is required in patients with renal or hepatic impairment. Omeprazole decreases the clearance of co-administered diazepam, phenytoin, and warfarin.

Administraton of omeprazole (as with other proton pump inhibitors) is associated with ventilator-associated pneumonia in critically ill patients.

Ondansetron

Uses

Ondansetron is used:

1. in the management of nausea and vomiting induced by chemotherapy and radiotherapy and
2. in the prevention and treatment of post-operative nausea and vomiting (PONV).

Chemical

A synthetic carbazole.

Presentation

As a clear, colourless aqueous solution in 2/4 ml ampoules containing 2 mg/ml ondansetron hydrochloride dihydrate.

It is also available as 4/8 mg tablets, as a strawberry-flavoured lyophilizate (4/8 mg), and as a suppository containing 16 mg of ondansetron.

Main action

Antiemetic.

Mode of action

Ondansetron is a highly selective antagonist at $5HT_3$ receptors and acts both centrally and peripherally. Emetogenic stimuli appear to cause release of 5HT in the small intestine and initiate a vomiting reflex by activating vagal afferents via $5HT_3$ receptors; ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also result in release of 5HT in the area postrema, promoting emesis via a central mechanism.

Routes of administration/doses

For prevention of chemotherapy- or radiotherapy-induced nausea and vomiting, the route of administration and dose of ondansetron should be flexible in the range of 8–32 mg/day. For prophylaxis against PONV, the drug may be administered as a single dose of 4 mg by intramuscular or slow intravenous injection. The paediatric dose is 0.1 mg/kg. Identical doses are recommended for treatment of established PONV.

Effects

CVS

Ondansetron has no demonstrable effects on the cardiovascular system.

RS

The drug has no effect on the ventilatory response to CO_2.

CNS

Ondansetron has no sedative effects and does not impair performance in psychomotor tests.

AS

Ondansetron has no effect on gastric motility, but does increase large bowel transit time.



Metabolic/other

Ondansetron has no effect on serum prolactin concentration or haemostatic function.

Toxicity/side effects

Constipation, headache, and flushing may occur. Bradycardia may occur following rapid intravenous administration. Rare cases of anaphylaxis have been reported.

Kinetics

Absorption

Ondansetron is passively and completely absorbed following oral administration and undergoes first-pass metabolism. Oral bioavailability of the drug is 60–65%. Peak plasma concentrations of approximately 30 ng/ml are achieved in about 1.5 hours following an 8 mg oral dose. Following intramuscular injection, peak plasma levels of 25 ng/ml are reached within 10 minutes and following a 4 mg intravenous dose, peak plasma levels of 65 ng/ml are achieved.

Distribution

The drug is 70–76% protein bound in the plasma; the V_D is 2 l/kg.

Metabolism

Ondansetron is extensively metabolized in the liver by multiple hepatic cytochrome P450 enzymes (CYP3A4, CYP2D6, and CYP1A2). The drug is metabolized by hydroxylation or N-demethylation of the indole nucleus, followed by conjugation with glucuronic acid or sulphate. Due to the number of enzyme systems involved, inhibition or deficiency of one (e.g. CYP2D6 deficiency/debrisoquine polymorphism) is normally compensated by other enzymes, resulting in little or no significant change in ondansetron clearance or dose requirement. Patients receiving CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin) may have increased clearance of ondansetron although this does not require dosage adjustment.

Excretion

Less than 5% of the drug is excreted unchanged in the urine. The clearance is 6.3 ml/kg/min and the elimination half-life is 3 hours.

Special points

In patients with renal impairment, both systemic clearance and volume of distribution are reduced following intravenous administration of ondansetron, resulting in an increase in elimination half-life (>4 hours). This increase is not clinically significant and no alteration of dose is required in patients with renal impairment. Hepatic impairment significantly reduces the clearance of the drug with prolonged elimination half-lives (15–32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. As a result of these effects, the dose of ondansetron should be limited to 8 mg/day in patients with hepatic impairment.

The drug may reduce the analgesic effect of tramadol.

Ondansetron contains less than 23 mg of sodium per dose.

Ondansetron may reduce the incidence of post-anaesthetic shivering.

Ondansetron may be used in combination with dexamethasone in the treatment of PONV.

Oseltamivir

Uses

Oseltamivir is used in the treatment of:

1. influenza virus infections and
2. for the prophylaxis of influenza virus infections.

Chemical

A synthetic ethyl ester.

Presentation

As 30/45/75 mg capsules and as a granulate powder for oral suspension at a concentration of 12 mg/ml of oseltamivir phosphate.

Main action

Oseltamivir is an antiviral agent active against influenza virus.

Mode of action

Oseltamivir phosphate is a pro-drug and requires ester hydrolysis to convert it into the active component: oseltamivir carboxylate. Oseltamivir carboxylate selectively inhibits influenza A and B neuraminidases *in vitro*, leading to inhibition of virus infection and replication.

Route of administration/doses

The adult oral dose for treatment of influenza infection is 150 mg in divided doses for 5 days. The dose in children aged between 1–12 years old is dependent on the patient's weight as follows: ≤15 kg (30 mg twice daily), >15–23 kg (45 mg twice daily), >23–40 kg (60 mg twice daily), >40 kg (75 mg twice daily), for 5 days. The dose for infants less than 12 months of age is 3 mg/kg (3–12 month olds), 2.5 mg/kg (1–3 month olds), 2 mg/kg (0–1 month old), twice daily for 5 days. The recommended dose for post-exposure prophylaxis is 75 mg once daily for 10 days in adults. The dose in children aged between 1–12 years old is dependent on the patient's weight as follows: ≤15 kg (30 mg once daily), >15–23 kg (45 mg once daily), >23–40 kg (60 mg once daily), >40 kg (75 mg once daily), for 10 days. The dose for infants less than 12 months of age is 3 mg/kg (3–12 month olds), 2.5 mg/kg (1–3 month olds), 2 mg/kg (0–1 month old), once daily for 10 days. Efficacy has been demonstrated when treatment initiation occurs within 2 days of first onset of symptoms (for treatment) or within 2 days of exposure to an infected individual (for prophylaxis).

Toxicity/side effects

The most commonly reported side effects are nausea (11%) and vomiting (8%) following use of the drug in adults. The incidence of these effects is higher in paediatric patients.

Kinetics

Absorption

The drug is readily absorbed from the gastrointestinal tract. Oseltamivir phosphate is converted by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate.

Distribution

The drug is 3% protein-bound in the plasma; the V_D at steady state is approximately 23 l.

Metabolism

Oseltamivir phosphate is extensively converted to oseltamivir carboxylate by hepatic esterases. It undergoes no further metabolism prior to elimination. Neither the pro-drug nor its active metabolite interacts with the hepatic cytochrome P450 system.

Excretion

Oseltamivir carboxylate is eliminated by renal excretion (>99%) via tubular secretion.

Special points

Dose reduction is recommended in patients with severe renal impairment. No dose adjustment is required in patients with hepatic impairment.

In vitro studies have demonstrated that virus isolates with reduced susceptibility to oseltamivir carboxylate can be recovered. Resistance to the drug is associated with mutations, resulting in amino acid substitutions in viral neuraminidase, haemagglutinin, or both. Resistant mutations are usually viral subtype-specific and may be naturally occurring (i.e. no prior exposure to oseltamivir required to cause resistance).

Oxycodone

Uses

Oxycodone is used for:

1. the treatment of moderate to severe pain in patients with cancer and post-operative pain and
2. in the treatment of severe pain requiring a strong opioid.

Chemical

A semi-synthetic opium alkaloid derivative.

Presentation

Oxycodone is available in immediate and controlled release preparations. The drug is available in 10 mg/ml and 50 mg/ml preparations for intravenous use; 5/10/20 mg capsules for oral use; and 1 mg/ml and 10 mg/ml as liquid formulations for oral use. The controlled release preparation is available in 5/10/20/40/80 mg tablets.

Main actions

The drug has opioid agonist activity, producing analgesia, anxiolysis, together with antitussive and sedative effects.

Mode of action

Oxycodone has an affinity for mu-, kappa-, and delta-opioid receptors. The mu-opioid receptor (MOP receptor) appears to be specifically involved in the mediation of analgesia. Opioids appear to exert their effects by interacting with pre-synaptic Gi-protein receptors, leading to hyperpolarization of the cell membrane by increasing K^+ conductance. Inhibition of adenylate cyclase, leading to reduced production of cyclic adenosine monophosphate and closure of voltage-sensitive calcium channels, also occurs. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Route of administration/doses

The drug may be administered orally, intravenously, or subcutaneously. The initial adult intravenous dose is 1–10 mg administered slowly over 1–2 minutes, titrated to effect. The initial adult oral dose is 5 mg 4–6-hourly, titrated to effect. 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone. There are no data available on the use of oxycodone in children. Dose reductions are required in elderly patients and those with renal and hepatic impairment.

Effects

CVS

Oxycodone has minimal effects on the cardiovascular system; the predominant effect is that of orthostatic hypotension secondary to a decrease in systemic vascular resistance, partly mediated by histamine release.

RS

The principle effect of the drug is respiratory depression with a decreased ventilatory response to hypoxia and hypercapnia. Oxycodone also has an antitussive action. Bronchoconstriction may occur with high doses of the drug.

CNS

Oxycodone is a powerful analgesic agent and may also cause drowsiness, relief of anxiety, and euphoria. Miosis is produced by the drug as a result of stimulation of the Edinger–Westphal nucleus. Increased muscle tone and seizure activity may occur with the use of high doses of oxycodone.

AS

Oxycodone decreases gastrointestinal motility. The drug may also cause nausea, vomiting, and constipation.

GU

The drug increases the tone of the ureters, bladder detrusor muscle, and sphincter, and may precipitate urinary retention.

Metabolic/other

The drug may cause histamine release, resulting in pruritus.

Toxicity/side effects

Respiratory depression, nausea and vomiting, hallucinations, and dependence may complicate the use of oxycodone.

Kinetics

Absorption

The oral bioavailability of oxycodone is 60–87%. The time to P_{max} is 1–1.5 hours following administration of immediate release oxycodone. The controlled release preparation has the same bioavailability, but due to a biphasic release pattern, the time to reach P_{max} is 3 hours.

Distribution

The V_D of oxycodone is 2.6 l/kg at steady state. Approximately 45% of the drug is bound to plasma proteins. The drug penetrates the placenta and is found in breast milk.

Metabolism

The drug undergoes extensive hepatic metabolism via CYP450 3A to noroxycodone and CYP450 2D6 to oxymorphone and various other conjugated glucuronides.

Excretion

Oxycodone and its metabolites undergo renal elimination. Up to 19% of free drug, up to 50% of conjugated oxycodone, and up to 14% of conjugated oxymorphone may be found in the urine. The elimination half-life of immediate release oxycodone is 3 hours and that of controlled release preparations 4.5 hours. Steady state is reached in approximately 24 hours. The clearance is 800 ml/min.

Special points

Oxycodone should be used with caution in the presence of hepatic failure as the drug may precipitate encephalopathy. In common with other opioids, oxycodone decreases the apparent MAC of co-administered volatile agents. The actions of the drug are all reversed by naloxone.

Prochlorperazine is chemically incompatible with oxycodone. The drug is compatible with hyoscine, dexamethasone, haloperidol, midazolam, and metoclopramide.

There is no evidence to suggest that blockade of CYP450 2D6 and CYP450 3A4 results in clinically significant effects.

Oxygen

Uses

Oxygen is used:

1. in the management of all forms of hypoxia (other than histotoxic)
2. as an adjunct in the management of shock and in the treatment of
3. carbon monoxide poisoning
4. pneumatosis coli
5. decompression sickness and
6. anaerobic infections.

Chemical

A gaseous inorganic element.

Presentation

As a compressed gas in cylinders at a pressure of 137 bar (13 700 kPa) at 15°C; the cylinders are black with white shoulders and are available in several different sizes. Those cylinders commonly used in hospital are C–J containing 170–6800 l, respectively. Size J cylinders are used for cylinder manifolds. The AZ cylinder is MRI compatible and contains 170 l. Oxygen is also available commercially in liquid form, one volume of liquid oxygen yielding 840 volumes of gaseous oxygen at 15°C and 1013 mb. Liquid oxygen is stored in a vacuum-insulated evaporator (VIE) which range in liquid capacity from 1600–18 675 l, depending on its size.

Oxygen is a colourless, odourless, tasteless gas which supports combustion and is explosive in the presence of grease. It has a molecular weight of 32, a specific gravity of 1.105, a critical temperature of –118.4°C, and a critical pressure of 50.8 atmospheres.

It is supplied at 99.5% purity with maximum amounts of carbon monoxide and carbon dioxide of 5.0 vpm and 300.0 vpm, respectively. Liquid oxygen appears pale blue.

Main action

The essential role of oxygen is in the process of oxidative phosphorylation.

Mode of action

Elemental oxygen is combined with hydrogen ions via mitochondrial cytochrome oxidase; the energy released is used for the synthesis of ATP.

Route of administration

Oxygen is administered by inhalation via fixed performance or variable performance devices. Depending on the device used, inspired concentrations of up to 100% may be achieved. Fixed performance devices include anaesthetic breathing systems with a suitably large reservoir and Venturi-operated devices (also known as high air flow oxygen enrichment, or HAFOE, devices). Variable performance devices include Hudson face masks, partial rebreathing masks, nasal cannulae, and nasal catheters. A number of factors determine the FiO_2 delivered by a variable performance device: gas flow rate, peak inspiratory flow rate, respiratory rate, and how tightly fitting the facemask is.

Effects

CVS

The administration of 100% oxygen causes a slight decrease in the heart rate (due to an effect on chemoreceptors), a slight increase in diastolic blood pressure, and a decrease of 8–20% in cardiac output due to myocardial depression. The coronary blood flow decreases, secondary to coronary arterial vasoconstriction. In contrast, the pulmonary vascular resistance and mean arterial pressure decrease.

RS

Mild respiratory depression (due to a decrease in sensitivity of the respiratory centre to carbon dioxide) results from the administration of 100% oxygen. Nitrogen is eliminated from the lungs within 2–3 minutes (leading to atelectasis subsequent to the loss of the 'splinting' effect of nitrogen), from the blood within 5 minutes, and from the body within 2 hours. The binding of oxygen with haemoglobin tends to displace carbon dioxide from the blood (the Haldane effect).

CNS

The administration of 100% oxygen causes cerebrovascular constriction (due to an increased sensitivity to adrenergic agonists), resulting in a decrease in cerebral blood flow.

Toxicity/side effects

The following toxic effects are associated with the use of high concentrations of oxygen:

1. carbon dioxide retention in patients with respiratory failure who are predominantly dependent upon a hypoxic drive to respiration
2. retrolental fibroplasia in neonates
3. acute oxygen toxicity (the Paul–Bert effect) may occur if hyperbaric 100% oxygen is used; the symptoms are altered mood, vertigo, loss of consciousness, and convulsions
4. chronic oxygen toxicity may occur when concentrations >60% are used for prolonged periods at atmospheric pressure; the symptoms of this are tracheobronchial irritation, sore throat, and substernal pain and the signs are pulmonary congestion, atelectasis, and a decreased vital capacity
5. prolonged administration of 100% oxygen may interfere with red blood cell formation.

Kinetics

Absorption

The gas is freely permeable through normal alveolar tissue.

Distribution

Oxygen is transported in the blood predominantly combined to haemoglobin; in addition, each 100 ml of plasma contains 0.3 ml of dissolved oxygen at normal atmospheric pressure and an FiO_2 of 0.21. When 100% oxygen is administered at atmospheric pressure, each 100 ml of plasma contains approximately 1.7 ml of dissolved oxygen. If 100% oxygen is administered at 3 atmospheres, approximately 6 ml of dissolved oxygen is contained within each 100 ml of plasma.

Metabolism

Occurs within mitochondria to produce carbon dioxide and water.

Excretion

As exhaled carbon dioxide and metabolic water.

Oxytocin

Uses

Oxytocin is used:

1. for the induction and acceleration of labour
2. to promote lactation and in the management of
3. missed and incomplete abortion and
4. post-partum haemorrhage.

Chemical

A naturally occurring polypeptide from the posterior lobe of the pituitary gland.

Presentation

As a clear solution for injection containing 5/10 Units/ml of synthetic oxytocin (which is free from vasopressin and extraneous animal protein) and in a fixed dose combination for injection containing 5 Units/ml of oxytocin and 500 micrograms of ergometrine maleate (which has a more sustained effect on the uterus than does oxytocin).

Main actions

Stimulation of uterine contraction.

Mode of action

Oxytocin is thought to act by binding to specific receptors on smooth muscle cells and increasing the permeability of the myometrial cell membrane to potassium ions, thereby decreasing the membrane potential and increasing the excitability of uterine smooth muscle.

Routes of administration/doses

Oxytocin is administered by intravenous infusion at a rate of 1.5–12 mUnits/min, titrated against the frequency and duration of uterine contractions. The intramuscular dose of the oxytocin-ergometrine preparation is 1 ml.

Effects

CVS

Bolus intravenous administration of oxytocin causes a decrease in the blood pressure that occurs within 30 seconds and lasts up to 10 minutes—this response is exaggerated in the anaesthetized subject. A reflex tachycardia and an increase in cardiac output by up to 1.5 l/min occur. ECG changes such as prolongation of the QT interval and T wave flattening may reflect poor coronary artery filling.

AS

Oxytocin has no effect on lower oesophageal sphincter pressure during pregnancy.

GU

Infusions of oxytocin increase the renal blood flow in animal models.

Metabolic/other

Oxytocin has an antidiuretic effect (exerted by a direct action on the renal tubules) which may, when it is administered in high doses with large volumes of electrolyte-free fluid, lead to water intoxication. Oxytocin also causes milk ejection by causing contraction of modified smooth muscle within the mammary gland, forcing milk from alveolar channels into large sinuses.

Toxicity/side effects

Oxytocin may cause uterine spasm and rupture, leading to fetal asphyxia when infused too rapidly. Anaphylactoid reactions to the drug have also been reported. Water intoxication has been described above.

Kinetics

Data are incomplete.

Absorption

Oxytocin is active when administered by any parenteral route, but is inactivated by chymotrypsin when administered orally.

Metabolism

Oxytocin is rapidly removed from the plasma by hydrolysisin the liver and kidney (by the action of oxytocinase).

Excretion

The elimination half-life is 1–7 minutes.

Special points

Oxytocin should not be infused through the same intravenous line as blood and plasma as rapid inactivation of the polypeptide by plasma oxytocinase occurs. Infusions of oxytocin may alter the action of co-administered suxamethonium, leading to a decrease in the fasciculations caused by the latter and an increased dose requirement for suxamethonium.



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Pancuronium

Uses

Pancuronium is used to facilitate intubation and controlled ventilation.

Chemical

A bis-quaternary aminosteroid.

Presentation

As a clear colourless solution for injection containing 2 mg/ml of pancuronium bromide. The solution has a pH of 4.

Main action

Pancuronium acts by competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction. The drug also has some pre-junctional action.

Route of administration/doses

The drug is administered intravenously. The ED_{95} of pancuronium is estimated to be 0.05 mg/kg. An initial dose of 0.05–0.1 mg/kg is recommended in adults, providing muscle relaxation for between 65–100 minutes. Endotracheal intubation can be achieved within 90–150 seconds of an intravenous dose with maximal resultant neuromuscular blockade achieved within 4 minutes following administration. Maintenance of neuromuscular blockade may be achieved with bolus doses of 0.01–0.02 mg/kg. An initial dose of 0.06–0.1 mg/kg is recommended in children. If pancuronium is administered after suxamethonium, then the initial intravenous dose of the former should be reduced to 0.02–0.06 mg/kg in both adults and children. The initial recommended dose in neonates is 0.03–0.04 mg/kg. The drug should not be given by infusion.

Effects

CVS

Pancuronium causes an increase in the heart rate, blood pressure, and cardiac output secondary to a vagolytic action. The systemic vascular resistance remains unchanged after the administration of the drug.

A slight fall in central venous pressure may occur.

RS

Neuromuscular blockade results in apnoea. Pancuronium has a very low potential for histamine release; bronchospasm is extremely uncommon.

AS

Reports of salivation have been noted.

Metabolic/other

Pancuronium may decrease the partial thromboplastin time and prothrombin time.

Toxicity/side effects

There have been rare reports of fatal anaphylactoid reactions with the administration of pancuronium. Cross-sensitivity may exist with vecuronium and rocuronium. A transient rash may occur following the administration of pancuronium.

Kinetics

Distribution

Pancuronium is 15–30% protein-bound in the plasma, predominantly to albumin and gamma globulin; the V_D is 0.241–0.280 l/kg, which is increased by approximately 50% in patients with cirrhosis. The drug does not cross the blood–brain barrier. Pancuronium has been shown to cross the placenta in small doses.

Metabolism

30–45% of an administered dose undergoes hepatic metabolism by deacetylation to 3-hydroxy-, 17-hydroxy-, and 3,17-hydroxy-derivatives with subsequent biliary excretion. The 3-hydroxy-derivative (up to 25% of an injected dose) has half the neuromuscular blocking activity of the parent drug compared to the other metabolites (less than 5% of an injected dose) which have approximately 50 times less potency than pancuronium.

Excretion

Pancuronium drug levels appear to decrease in a triphasic manner. 40–50% of the dose is excreted in the urine (80% as unchanged drug), with 5–11% appearing in the bile. The clearance is 1.10–2.22 ml/kg/min and the elimination half-life is 69–161 minutes (decreased by 22% and doubled, respectively, in patients with cirrhosis).

Special points

The duration of action of pancuronium, in common with other non-depolarizing relaxants, is prolonged by hypokalaemia, hypocalcaemia, hypermagnesaemia, hypoproteinaemia, dehydration, acidosis, and hypercapnia. The following drugs, when co-administered with pancuronium, increase the effect of the latter: volatile anaesthetic agents, induction agents, fentanyl, suxamethonium, diuretics, calcium channel blockers, alpha- and beta-adrenergic antagonists, protamine, lidocaine, metronidazole, and the aminoglycoside antibiotics. Pancuronium appears to decrease the MAC of halothane; it also tends to counteract the depressant effect of halothane on the blood pressure.

Due to the increased V_D seen in patients with cirrhosis, the initial dose to achieve adequate muscle relaxation may be higher. However, the duration of action of the drug may be prolonged in patients with cirrhosis, biliary dysfunction, and renal impairment. The dose should be reduced in the presence of renal impairment.

The use of pancuronium appears to be safe in patients susceptible to malignant hyperpyrexia.

Paracetamol

Uses

Paracetamol is used:

1. as an analgesic for the relief of pain of mild to moderate severity and
2. as an antipyretic agent.

Chemical

As acetanilide derivative.

Presentation

As tablets and suppositories containing 60/125/250/500 mg of paracetamol and a syrup containing 24/50 mg/ml. A number of fixed dose combinations with codeine, dihydrocodeine, pentazocine, and metoclopramide are also available. The drug is often a component of proprietary cold cures. A dispersible tablet form is available, but has a high sodium content due to the presence of sodium bicarbonate. An intravenous preparation for infusion is available containing 10 mg/ml of paracetamol is available in 50 ml and 100 ml vials. The intravenous preparation also contains cysteine hydrochloride monohydrate, disodium phosphate dihydrate, sodium hydroxide, and mannitol. The sodium content is less than 23 mg per 100 ml. The preparation is sealed in a glass vial also containing argon as the drug is unstable in an oxygen-rich environment. The drug should be infused over a 15-minute period. An intravenous preparation containing the pro-drug propacetamol, 1 g of which is equivalent to 500 mg of paracetamol, is also available.

Main action

Analgesic and antipyretic.

Mode of action

The mode of action of paracetamol is poorly understood although there is evidence of activity involving prostaglandin synthesis inhibition, and serotonergic and cannabinoid pathways. The drug inhibits COX isoenzymes, COX-1 and COX-2, particularly in areas of low inflammation (cf. non-steroidal anti-inflammatory drugs). Prostaglandin synthesis within the central nervous system is inhibited which accounts for the antipyretic effect of the drug; specifically, it inhibits the synthesis of the E series of prostaglandins that are normally produced in the anterior hypothalamus in response to pyrogens. There is evidence that paracetamol enhances inhibitory serotonergic pain pathways as well as inhibiting the uptake of anandamide, an endocannabinoid, involved in nociception. The drug also acts peripherally by blocking impulse generation within the bradykinin-sensitive chemoreceptors responsible for the generation of afferent nociceptive impulses.

Routes of administration/doses

The dose for adolescents and adults weighing more than 50 kg is 500 mg–1 g 4–6-hourly (maximum daily dose 4 g) for the oral, rectal, and intravenous routes. Analgesic doses in children range from 60 to 90 mg/kg/day in divided doses, depending on age and route of administration. Analgesic doses in neonates range from 30 to 60 mg/kg/day in divided doses, depending on post-conceptual age and route of administration. A loading dose may be given.

Effects

CNS

The maximum analgesic effect of paracetamol appears to be greater than that of any other non-opioid analgesic.

AS

Paracetamol is occasionally used as a model for drug absorption as its rate of absorption is proportional to the gastric emptying rate. Drugs which alter gastric emptying alter the rate of paracetamol absorption. The drug has no effect on the liver unless taken in overdose and does not cause gastric ulceration.

Metabolic/other

The drug potentiates the effect of antidiuretic hormone. It has a dose-dependent effect on platelets, causing reduced aggregation via platelet COX-1 inhibition and a subsequent decrease in thromboxane A2 synthesis. This degree of inhibition is unlikely to cause clinically significant bleeding.

Toxicity/side effects

Gastrointestinal disturbances, skin reactions, and idiosyncratic haemopoietic disorders (thrombocytopaenia, neutropaenia) may occur with therapeutic doses. Approximately 5% of patients who are allergic to aspirin show cross-sensitivity to paracetamol.

Kinetics

Absorption

The drug is rapidly absorbed from the upper gastrointestinal tract; the bioavailability when administered by the oral route is 63–89% due to first-pass metabolism. Absorption is variable when administered rectally and the bioavailability by this route is 24–98% of that observed after oral administration.

Distribution

At therapeutic levels, paracetamol is 0–5% protein-bound in the plasma; the V_D is 0.7–1 l/kg. Being a non-ionized, lipid-soluble substance, paracetamol penetrates tissues and the blood–brain barrier well. The drug crosses the placenta.

Metabolism

Occurs predominantly in the liver, 80–90% being metabolized to glucuronide (60–80%) and sulphate (20–30%) and 10% by cytochrome P450 (CYP2E1) to a highly reactive intermediate metabolite (N-acetyl-p-benzo-quinoneimine (NAPQI)) which in turn is inactivated by conjugation with glutathione. In the central nervous system, paracetamol is metabolized to P-aminophenol and then to N-arachidonoylphenolamine.

Excretion

1–5% is excreted unchanged in the urine; the glucuronide and sulphate metabolites are actively secreted in the renal tubules at low concentrations and actively reabsorbed at high concentrations. The clearance is 5 ml/kg/min and the elimination half-life is 2–4 hours in normal adults, 4–5 hours in neonates, and 11 hours in premature neonates.

Special points

Paracetamol should be used with caution in patients with renal or hepatic impairment. The dose interval should be increased in patients with severe renal impairment. Paracetamol is removed by haemodialysis. The drug may lead to an increase in the INR of patients taking warfarin, possibly due to reduced synthesis of vitamin K-dependent clotting factors.

Hepatic damage occurs readily with doses exceeding 15 g of the drug; with toxic doses, the supply of glutathione becomes depleted and the highly reactive intermediate metabolite (NAPQI) combines with hepatic cell membranes, leading eventually to centrilobular necrosis. N-acetylcysteine (NAC) and methionine act as alternative supplies of glutathione and can protect against paracetamol-induced liver damage if administered within 10–12 hours of ingestion of paracetamol. A treatment intervention graph is widely available. The major complication is fulminant hepatic failure (with or without acute renal failure) usually occurring at 2–7 days. Liver function tests are a poor prognostic indicator under these circumstances. Criteria for referral to a specialist liver centre are: encephalopathy, INR >3 on day 2 (>4.5 on day 3 or any increase thereafter), creatinine >200 μmol/l or oliguria, arterial pH <7.3, hypoglycaemia. Patients may be considered for transplantation if arterial pH <7.3 (or <7.25 if NAC administered) or the combination of prothrombin time >100 seconds, creatinine >300 μmol/l, and grade III encephalopathy. The following are associated with a poor outcome: bilirubin levels >4 mg/100 ml, INR >2.2, lactate >3.5 mmol/l at 4 and 12 hours, low factor V levels.

Methionine has been added to paracetamol preparations to decrease the risk of hepatotoxicity in overdosage.

Penicillin

Uses

Penicillin is used in the treatment of infections of:

1. the respiratory tract
2. ear, nose, and throat
3. skin, bone, soft tissues, and wounds and in the treatment of
4. gonorrhoea
5. meningitis and
6. subacute bacterial endocarditis.

Chemical

The prototype penicillin.

Presentation

The preparation for oral use is phenoxymethylpenicillin (penicillin V) which is presented as 125/250 mg tablets and in an elixir as the potassium salt. The parenteral preparation is benzylpenicillin (penicillin G) which is a white crystalline powder presented in vials containing 0.3/0.6/3/6 g of sodium benzylpenicillin.

Main actions

Penicillin is a bactericidal antibiotic with a narrow spectrum of activity, which includes *Streptococcus*, *Neisseria*, *Haemophilus*, *Corynebacterium*, *Bacillus*, *Clostridium*, *Listeria*, and *Treponema* spp., some sensitive staphylococcal strains, and oral anaerobes. Penicillin is destroyed by beta-lactamases produced by some strains of

Pseudomonas, *Enterobacteriaceae*, and *Bacteroides*.

Mode of action

Penicillin binds specifically to penicillin-binding proteins (transpeptidases and carboxypeptidases) in the bacterial cell wall and prevents peptidoglycan cross-linking, thereby decreasing the mechanical stability of the bacterial cell wall.

Routes of administration/doses

The adult oral dose is 125–250 mg 4–6-hourly; the corresponding intravenous and intramuscular dose is 0.6–4.8 g/day in 2–4 divided doses. 1 mega Unit is 600 mg. Penicillin may also be administered intrathecally.

Effects

Metabolic/other

High doses of benzylpenicillin may produce hypernatraemia and hypokalaemia.

Toxicity/side effects

Gastrointestinal disturbances, allergic phenomena (including anaphylaxis), rashes, and haemolytic anaemia may occur with the use of the drug. High parenteral doses of penicillin may cause neuropathy and nephropathy.

Kinetics

Absorption

15–30% of an oral dose of penicillin G (the drug is unstable under acid conditions) and 60% of an oral dose of penicillin V is absorbed. The pharmacokinetics after absorption is similar for both preparations.

Distribution

Penicillin is 59–67% protein-bound in the plasma, predominantly to albumin; the V_D is 0.32–0.81 l/kg.

Metabolism

Penicillin is metabolized to penicilloic acid which is inactive with subsequent transformation to penamaldic and penicillenic acid.

Excretion

60–90% of a dose is excreted in the urine by active tubular secretion; up to 25% is excreted unchanged. The elimination half-life is 0.7 hours.

Special points

Penicillin is removed by haemodialysis.

Pethidine

Uses

Pethidine is used:

1. for premedication
2. as an analgesic in the management of moderate to severe pain and
3. as an antispasmodic agent in the treatment of renal and biliary colic.

Chemical

A synthetic phenylpiperidine derivative.

Presentation

As 50 mg tablets and a clear, colourless solution for injection containing 10/50 mg/ml of pethidine hydrochloride.

Main actions

Analgesia and respiratory depression.

Mode of action

Pethidine is an agonist at mu- and kappa-opioid receptors. Opioids appear to exert their effects by increasing intracellular calcium concentration which, in turn, increases potassium conductance and hyperpolarization of excitable cell membranes. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routes of administration/doses

The adult oral dose is 50–150 mg 4-hourly; the corresponding dose by the intramuscular route is 25–150 mg and by the intravenous route 25–100 mg. Pethidine may also be administered via the epidural route; a dose of 25 mg is usually employed. The drug acts within 15 minutes when administered orally and within 10 minutes when administered intramuscularly; the duration of action is 2–3 hours.

Effects

CVS

Pethidine causes orthostatic hypotension due to the combination of histamine release and alpha-adrenergic blockade that it produces. The drug also has a mild quinidine-like effect and anticholinergic properties, which may lead to the development of a tachycardia.

RS

The drug is a potent respiratory depressant, having a greater effect on tidal volume than on the respiratory rate. Pethidine obtunds the ventilatory response to both hypoxia and hypercapnia. Chest wall rigidity may occur with the use of the drug. It has little antitussive activity.

CNS

Pethidine is one tenth as potent an analgesic as morphine. It appears to cause more euphoria and less nausea and vomiting than an equipotent dose of morphine. Miosis and corneal anaesthesia follow the use of the drug.

AS

In common with other opioids, pethidine decreases the rate of gastric emptying. The drug appears to cause a less marked increase in bile duct pressure and less depression of intestinal activity (and therefore constipation) than equipotent doses of morphine.

GU

The drug decreases ureteric tone; it may increase the amplitude of contractions of the pregnant uterus.

Metabolic/other

Pethidine increases ADH secretion and decreases adrenal steroid secretion.

Toxicity/side effects

Respiratory depression, nausea and vomiting, hallucinations, and dependence may complicate the use of pethidine. The drug evokes less histamine release than morphine.

Kinetics

Absorption

The bioavailability, when administered orally, is 45–75% due to a significant first-pass effect. The drug has a bioavailability of 100% when administered intramuscularly (into the deltoid muscle).

Distribution

Pethidine is 49–67% protein-bound in the plasma; the V_D is 3.5–5.3 l/kg. The drug crosses the placenta; the mean cord blood concentration at delivery is 75–90% of the maternal venous concentration.

Metabolism

Occurs in the liver by N-demethylation to norpethidine and by hydrolysis to pethidinic acid; norpethidine is further hydrolyzed to norpethidinic acid. The acid metabolites are further conjugated prior to excretion. Norpethidine may accumulate in the presence of renal failure and has 50% the analgesic potency of the parent compound and marked convulsant properties.

Excretion

1–25% of the administered dose is excreted unchanged in the urine, dependent upon the urinary pH. Norpethidine is excreted in the urine; accumulation may occur in the presence of renal or hepatic impairment. The clearance is 12–22 ml/min/kg and the elimination half-life is 2.4–7 hours. The clearance is reduced by the co-administration of halothane.

Special points

Pethidine may precipitate a severe hypertensive episode in patients receiving MAOIs. The drug reduces the apparent MAC of co-administered volatile agents. By convention, pethidine is used in asthmatic patients although there is no published evidence that the drug causes bronchospasm less frequently than morphine in this group of patients.

Pethidine effectively inhibits post-anaesthetic shivering.

Phenelzine

Uses

Phenelzine is used in the treatment of:

1. non-endogenous depression and
2. phobic disorders.

Chemical

A substituted hydrazine.

Presentation

As tablets containing 15 mg of phenelzine sulphate.

Main action



Antidepressant.

Mode of action

Phenelzine is an irreversible inhibitor of mitochondrial monoamine oxidase, an enzyme involved in the metabolism of catecholamines and 5-hydroxytryptamine. It is assumed that the antidepressant activity of the drug is related to the increased concentration of monoamines in the central nervous system that results from the use of the drug.

Routes of administration/doses

The adult oral dose is 15 mg 6–8-hourly; this is reduced once a satisfactory response has been obtained. The maximum inhibition of enzyme activity is achieved within a few days, but the antidepressant effect of the drug may take 3–4 weeks to become established.

Effects

CVS

The predominant effect of the drug is orthostatic hypotension; MAOIs were formerly used as antihypertensive agents.

CNS

Phenelzine is an effective antidepressant which may also produce stimulation of the central nervous system, resulting in tremor and insomnia.

The MAOIs suppress REM sleep very effectively.

AS

Constipation occurs commonly with the use of the drug; the mechanism of this effect is unknown.

Metabolic/other

Inappropriate secretion of ADH has been reported in association with the use of phenelzine.

Toxicity/side effects

Disturbances of the central nervous system (including convulsions and peripheral neuropathy), anticholinergic side effects, and hepatotoxicity may complicate the use of the drug. More importantly, a host of serious and potentially fatal interactions may occur between MAOIs and tyramine-containing substances, sympathomimetic agents, and central nervous system depressants (v.i.).

Kinetics

Data are incomplete.

Absorption

Phenelzine is readily absorbed when administered orally.

Metabolism

80% of the dose is metabolized by oxidation and hydroxylation to phenylacetic acid and parahydroxyphenylacetic acid. The drug may inhibit its own metabolism.

Excretion

Occurs predominantly in the urine as free and unconjugated aromatic forms of the drug.

Special points

MAOIs demonstrate several important drug interactions:

1. drugs, such as pethidine, fentanyl, morphine, and barbiturates, whose action is terminated by oxidation, have a more profound and prolonged effect in the presence of MAOIs; this is particularly marked in the case of pethidine. Marked hyperpyrexia, possibly due to 5HT release, may also occur when pethidine is administered to a patient who is already receiving MAOIs
2. indirectly acting sympathomimetic agents (e.g. ephedrine) produce an exaggerated pressor response in the presence of co-administered MAOIs; severe hypertensive episodes (which are best treated with phentolamine) may result from this interaction
3. MAOIs markedly exaggerate the depressant effects of volatile anaesthetic agents on the blood pressure and central nervous system
4. MAOIs inhibit plasma cholinesterase and may, therefore, prolong the duration of action of co-administered suxamethonium
5. MAOIs may also potentiate the effects of antihypertensive and hypoglycaemic agents, anti-Parkinsonian drugs, and local anaesthetics.

A period of 2 weeks is required to restore amine metabolism to normal after the cessation of administration of phenelzine. This is the recommended period that should elapse between discontinuation of MAOI therapy and elective surgery. Post-operative analgesia for patients who are still receiving MAOI therapy has been safely provided using chlorpromazine and codeine.

Phenoxybenzamine

Uses

Phenoxybenzamine is used in the treatment of:

1. hypertensive crises
2. Raynaud's phenomenon and
3. in the preoperative preparation of patients due for the removal of a phaeochromocytoma.

Chemical

A tertiary amine which is a haloalkylamine.

Presentation

As 10 mg tablets and a clear, colourless solution for injection containing 50 mg/ml of phenoxybenzamine hydrochloride.

Main actions

Vasodilatation (predominantly arterial).

Mode of action

Phenoxybenzamine acts via a highly reactive carbonium ion derivative which binds covalently to alpha-adrenergic receptors to produce irreversible competitive alpha-blockade. The drug increases the rate of peripheral turnover of noradrenaline and the amount of noradrenaline released per impulse by blockade of pre-synaptic alpha-2 receptors. Haloalkylamines also inhibit the response to serotonergic, histaminergic, and cholinergic stimulation.

Routes of administration/doses

The adult dose by the oral route is 10–60 mg/day in divided doses. The corresponding dose by intravenous infusion (diluted in glucose or saline) over 1 hour is 10–40 mg. After intravenous administration, the drug acts in 1 hour and has duration of action of 3–4 days.

Effects

CVS

Phenoxybenzamine produces a decrease in the peripheral vascular resistance, which leads to a decrease in the diastolic blood pressure and pronounced orthostatic hypotension. A reflex tachycardia and an increase in cardiac output follow the administration of the drug. Phenoxybenzamine inhibits catecholamine-induced cardiac dysrhythmias. The drug causes a shift of fluid from the interstitial to the vascular compartment due to vasodilatation of pre- and post-capillary resistance vessels.

CNS

The drug decreases cerebral blood flow only if marked hypotension occurs. Motor excitability may follow the administration of phenoxybenzamine; however, sedation is the usual effect observed. Miosis occurs commonly.

AS

Phenoxybenzamine produces little change in gastrointestinal tone or splanchnic blood flow.

GU

The drug causes little alteration of renal blood flow; it decreases the motility of the non-pregnant uterus.

Toxicity/side effects

Dizziness, sedation, a dry mouth, paralytic ileus, and impotence may result from the use of phenoxybenzamine. The drug is irritant if extravasation occurs.

Kinetics

Data are incomplete.

Absorption

Phenoxybenzamine is incompletely absorbed after oral administration; the bioavailability by this route is 20–30%.

Distribution

The drug is highly lipophilic.

Metabolism

Phenoxybenzamine is predominantly metabolized in the liver by deacetylation.

Excretion

Occurs via the urine and bile; the half-life is 24 hours.

Special points

Systemic administration of the drug may lead to an increase in the systemic absorption of co-administered local anaesthetic agents. Phenoxybenzamine causes marked congestion of the nasal mucosa and this may make nasal instrumentation more traumatic if topical vasoconstrictors are not used.

Phentolamine

Uses

Phentolamine is used for:

1. the diagnosis and perioperative management of patients with phaeochromocytoma
2. the acute treatment of hypertension occurring during anaesthesia and
3. the treatment of left ventricular failure complicating myocardial infarction.

Chemical

An imidazoline.

Presentation

As a clear solution for injection containing 10 mg/ml of phentolamine mesilate.

Main actions

Hypotension, positive inotropism, and chronotropism.

Mode of action

Phentolamine acts by transient, competitive, alpha-adrenergic blockade (it is 3–5 times as active at alpha-1 as at alpha-2 receptors); it also has some beta-adrenergic agonist and anti-serotonergic activity.

Routes of administration/doses

The adult intramuscular dose for the control of paroxysmal hypertension is 5–10 mg; the drug may also be administered by intravenous infusion (diluted in glucose or saline) at the rate of 0.1–0.2 mg/min.

Effects

CVS

Phentolamine causes a marked reduction in the systemic vascular resistance, producing a decrease in blood pressure and a reflex tachycardia. The drug has a positive inotropic action, which is probably an indirect effect due to alpha-2 blockade leading to noradrenaline release. The coronary blood flow increases; the drug also has class I antiarrhythmic effects. In patients with heart failure, phentolamine causes an increase in the heart rate and cardiac output, with a concomitant decrease in the pulmonary arterial pressure, systemic vascular resistance, and left ventricular end-diastolic pressure.

RS

The drug increases the vital capacity, FEV1, and maximum breathing capacity in normal subjects, and prevents histamine-induced bronchoconstriction. Respiratory tract secretions are increased by the drug. Phentolamine is a pulmonary arterial vasodilator.

AS

The drug increases salivation, gastric acid, pepsin secretion, and gastrointestinal motility.

Metabolic/other

The drug increases insulin secretion.

Toxicity/side effects

Phentolamine is generally well tolerated, but may cause orthostatic hypotension, dizziness, abdominal discomfort, and diarrhoea. Cardiovascular collapse and death have followed the administration of phentolamine when it is used as a diagnostic test for phaeochromocytoma.

Kinetics

Data are incomplete.

Absorption

The bioavailability is 20% when administered orally.

Metabolism

The drug is extensively metabolized.

Excretion

10% of the dose is excreted in the urine unchanged. The plasma half-life is 10–15 minutes.

Special points

Phentolamine causes marked congestion of the nasal mucosa and this may make nasal instrumentation more traumatic if topical vasoconstrictors are not used.

Phenylephrine

Uses

Phenylephrine is used as an adjunct in the treatment of:

1. hypotension occurring during general or spinal anaesthesia
2. as a nasal decongestant and
3. as a mydriatic agent.

Chemical

A synthetic sympathomimetic amine.



Presentation

As a clear solution containing 10 mg/ml of phenylephrine hydrochloride.

Main action

Peripheral vasoconstriction.

Mode of action

Phenylephrine is a direct-acting sympathomimetic agent that has agonist effects at alpha-1 adrenoceptors. The drug does not affect beta-adrenoceptors.

Routes of administration/doses

Phenylephrine may be administered subcutaneously or intramuscularly in a dosage of 2–5 mg with further doses titrated to response. The drug may be administered intravenously following dilution in 0.9% sodium chloride (e.g. 10 mg of phenylephrine diluted in 100 ml of 0.9% sodium chloride yields a 100 micrograms/ml solution which can be diluted further, producing a 25 micrograms/ml solution) in 50–100 micrograms boluses. When administered intravenously, it has duration of action of 5–10 minutes. When administered intramuscularly or subcutaneously, it has duration of action of up to 1 hour.

Effects

CVS

Phenylephrine causes a rapid increase in the systolic and diastolic blood pressures due to an increase in the systemic vascular resistance. A reflex bradycardia occurs, which may cause a decrease in cardiac output.

RS

The drug is not known to cause bronchodilatation or act as a respiratory stimulant.

CNS

Phenylephrine has no stimulatory effects on the central nervous system. Phenylephrine causes mydriasis.

GU

The drug reduces uterine artery blood flow via its effect at alpha-adrenoceptors. Renal blood flow is decreased.

Metabolic/other

The drug may cause alterations in glucose metabolism.

Toxicity/side effects

Headaches, sweating, hypersalivation, tremor, and urinary retention may complicate the use of the drug. Extravascular injection of the drug may lead to tissue necrosis at the injection site.

Kinetics

There are no quantitative data available.

Metabolism

The drug is metabolized in the gastrointestinal tract and liver by monoamine oxidase.

Special points

Excessive hypertension may occur when phenylephrine is administered to patients with hyperthyroidism or those receiving monoamine oxidase inhibitors. Patients receiving cardiac glycosides, tricyclic antidepressants, or quinidine are at an increased risk of developing dysrhythmias when phenylephrine is administered.

Phenytoin

Uses

Phenytoin is used:

1. in the prophylaxis and treatment of generalized tonic-clonic and partial epilepsies and in the treatment of
2. fast atrial and ventricular dysrhythmias resulting from digoxin toxicity and
3. trigeminal neuralgia.

Chemical

A hydantoin derivative.

Presentation

As 25/50/100/300 mg capsules, a syrup containing 6 mg/ml, and as a clear, colourless solution for injection containing 50 mg/ml of phenytoin sodium.

Main actions

Anticonvulsant and antiarrhythmic.

Mode of action

Phenytoin has membrane stabilizing activity and slows inward sodium and calcium ion flux during depolarization in excitable tissue; it also delays outward potassium ion flux. There appears to be a high-affinity binding site within the central nervous system for phenytoin, which suggests the existence of an endogenous ligand.

Routes of administration/doses

The adult oral dose is 200–600 mg/day; a small dose should be used initially and gradually increased thereafter. The corresponding intramuscular dose is 100–200 mg 4-hourly for 48–72 hours, decreasing to 300 mg daily. The intravenous loading dose for the management of epilepsy is 10–15 mg/kg (administered slowly), followed by a maintenance dose of 100 mg 6–8-hourly. When used in the treatment of cardiac dysrhythmias, the corresponding intravenous dose is 3.5 mg/kg. The therapeutic range is 10–20 mg/l.

Effects

CVS

Phenytoin exhibits class I antiarrhythmic properties and enhances atrio-ventricular nodal conduction. Hypotension may complicate rapid intravenous administration of the drug; complete heart block, ventricular fibrillation, and asystole have also been reported under these circumstances.

CNS

80% of newly diagnosed epileptics can be controlled with phenytoin monotherapy. The drug acts as an anticonvulsant by stabilizing rather than raising the seizure threshold and by preventing the spread of seizure activity rather than by abolishing a primary discharging focus.

Metabolic/other

Hyperglycaemia, hypocalcaemia, and alterations in liver function tests have been described consequent to phenytoin therapy. The drug suppresses ADH secretion.

Toxicity/side effects

Phenytoin has both idiosyncratic and concentration-dependent side effects. The idiosyncratic side effects include acne, gingival hyperplasia, hirsutism, coarsened facies, folate-dependent megaloblastic anaemia and other blood dyscrasias, osteomalacia, erythroderma, lymphadenopathy, systemic lupus erythematosus, hepatotoxicity, and allergic phenomena. The concentration-dependent side effects include nausea and vomiting, drowsiness, behavioural disturbances, tremor, ataxia, nystagmus, paradoxical seizures, peripheral neuropathy, and cerebellar damage. The drug is irritant if extravasation occurs when given intravenously and may cause muscular damage when administered intramuscularly.

Kinetics

Absorption

Absorption is very slow by both the intramuscular and oral routes. The oral bioavailability is 85–95%.

Distribution

Phenytoin is 90–93% protein-bound in the plasma; the V_D is 0.5–0.7 l/kg.

Metabolism

There is a large genetic variation in the rate of metabolism of phenytoin, which occurs in the liver predominantly to a hydroxylated derivative which is subsequently conjugated to glucuronide. Phenytoin exhibits zero-order elimination kinetics just above the therapeutic range; the implication of this is that the dose required to produce a plasma concentration within the therapeutic range is close to that which will produce toxicity.

Excretion

70–80% of the dose is excreted in the urine by active tubular secretion as the major metabolite; 5% is excreted unchanged. The clearance is 5.5–9.5 ml/kg/day and the elimination half-life is 9–22 hours in the first-order kinetics range; the latter increases at higher dose ranges when the capacity of the hepatic mono-oxygenase system becomes saturated. The dose of phenytoin should be reduced in the presence of hepatic impairment, but renal impairment requires little alteration of dosage (despite the fact that the free fraction of the drug increases in the presence of uraemia, an increase in the clearance and V_D tend to offset this).

Special points

Phenytoin is a potent enzyme inducer and demonstrates a plethora of drug interactions, amongst which the most important are the precipitation of phenytoin toxicity by metronidazole and isoniazid and a reduced effectiveness of benzodiazepines, pethidine, and warfarin caused by the co-administration of phenytoin. The drug may also decrease the MAC of volatile agents and enhance the central nervous system toxicity of local anaesthetics; it appears to increase the dose requirements of all the non-depolarizing relaxants (with the exception of atracurium) by 60–80%.

The parenteral preparation of phenytoin precipitates in the presence of most crystalloid solutions.

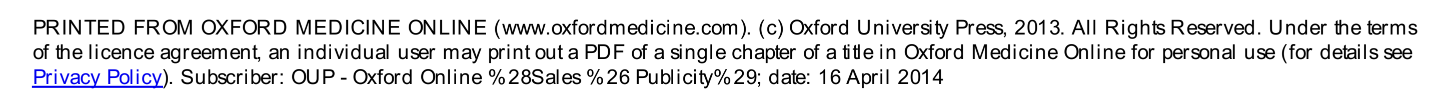
The drug is not removed by dialysis.

Piperacillin

Uses

Piperacillin is used in the treatment of:

1. urinary and respiratory tract infections
2. intra-abdominal and biliary tract sepsis
3. gynaecological and obstetric infections
4. infections of skin, soft tissue, bone, and joints
5. septicaemia



6. meningitis and for
7. perioperative prophylaxis.

Chemical

A semi-synthetic penicillin.

Presentation

In vials containing 1/2 g and infusion bottles containing 4 g of piperacillin sodium. A fixed dose combination with tazobactam is also available.

Main actions

Piperacillin is a bactericidal broad-spectrum antibiotic that is effective against many beta-lactamase-producing organisms. *In vitro*, it shows activity against the Gram-negative organisms: *Escherichia coli*, *Haemophilus influenzae*, and *Klebsiella*, *Neisseria*, *Proteus*, *Shigella*, and *Serratia* spp.; anaerobes including *Bacteroides* and *Clostridium* spp. and the Gram-positive enterococci, *Staphylococcus*, and *Streptococcus* spp. It is particularly effective against *Pseudomonas*, indole-positive *Proteus*, *Streptococcus faecalis*, and *Serratia marcescens*.

Mode of action

Piperacillin binds to cell wall penicillin-binding proteins (PBPs) and inhibits their activity; specifically, it affects PBP 1A/B which are involved in the cross-linking of cell wall peptidoglycans, PBP 2 which is involved in the maintenance of the rod shape, and PBP 3 which is involved in septal synthesis.

Routes of administration/doses

The adult intravenous dose is 4 g 6–8-hourly (each gram should be infused over 3–5 minutes) and the intramuscular dose 2 g 6–8-hourly.

Effects

Metabolic/other

Piperacillin has a lower sodium content than other disodium penicillins and causes less fluid and electrolyte derangements; serum potassium levels may decrease after the administration of the drug.

Toxicity/side effects

Gastrointestinal upsets, abnormalities of liver function tests, allergic reactions, and transient leucopaenia and neutropaenia may complicate the use of the drug. Deterioration in renal function has been reported in patients with pre-existent severe renal impairment treated with piperacillin.

Kinetics

Absorption

Piperacillin is poorly absorbed when administered orally and is hydrolyzed by gastric acids.

Distribution

The drug is 16% protein-bound in the plasma; the V_D is 0.32 l/kg. High concentrations are found in most tissues and body fluids.

Metabolism

Piperacillin is not metabolized in man.

Excretion

20% is excreted in the bile; the remainder is excreted in the urine by glomerular filtration and tubular secretion. The elimination half-life is 36–72 minutes.

Special points

The dose of piperacillin should be reduced in the presence of renal impairment; the drug is 30–50% removed by haemodialysis.

Prednisolone

Uses

Prednisolone is used:

1. as replacement therapy in adrenocortical deficiency states and in the treatment of
2. allergy and anaphylaxis
3. hypercalcaemia
4. asthma
5. a panoply of autoimmune disorders
6. some forms of red eye and
7. in leukaemia chemotherapy regimes and
8. for immunosuppression after organ transplantation.

Chemical

A synthetic glucocorticosteroid.

Presentation

As 1/2.5/5/20 mg tablets of prednisolone, a solution for injection containing 25 mg/ml of prednisolone acetate, and as eye/ear drops and retention enemas.

Main actions

Anti-inflammatory.

Mode of action

Corticosteroids act by controlling the rate of protein synthesis; they react with cytoplasmic receptors to form a complex which directly influences the rate of RNA transcription. This directs the synthesis of lipocortins.

Routes of administration/doses

The adult oral dose is 5–60 mg/day in divided doses, using the lowest dose that is effective and on alternate days, if possible, to limit the development of side effects. The intramuscular or intra-articular dose is 25–100 mg once or twice weekly.

Effects

CVS

In the absence of corticosteroids, vascular permeability increases, small blood vessels demonstrate an inadequate motor response, and cardiac output decreases. Steroids have a positive effect on myocardial contractility and cause vasoconstriction by increasing the number of alpha-1 adrenoreceptors and beta-adrenoreceptors and stimulating their function.

CNS

Corticosteroids increase the excitability of the central nervous system; the absence of glucocorticoid leads to apathy, depression, and irritability.

AS

Prednisolone increases the likelihood of peptic ulcer disease. It decreases the gastrointestinal absorption of calcium.

GU

Prednisolone has weak mineralocorticoid effects and produces sodium retention and increased potassium excretion; the urinary excretion of calcium is also increased by the drug. The drug increases the glomerular filtration rate and stimulates tubular secretory activity.

Metabolic/other

Prednisolone exerts profound effects on carbohydrate, protein, and lipid metabolism. Glucocorticoids stimulate gluconeogenesis and inhibit the peripheral utilization of glucose; they cause a redistribution of body fat, enhance lipolysis, and also reduce the conversion of amino acids to protein. Prednisolone is a potent anti-inflammatory agent which inhibits all stages of the inflammatory process by inhibiting neutrophil and macrophage recruitment, blocking the effect of lymphokines, and inhibiting the formation of plasminogen activator. Corticosteroids increase red blood cell, neutrophil, and haemoglobin concentrations whilst depressing other white cell lines and the activity of lymphoid tissue.

Toxicity/side effects

Consist of an acute withdrawal syndrome and a syndrome (Cushing's) produced by prolonged use of excessive quantities of the drug. Cushing's syndrome is characterized by growth arrest, a characteristic appearance consisting of central obesity, a moon face, and buffalo hump, striae, acne, hirsutism, skin and capillary fragility together with the following metabolic derangements: altered glucose tolerance, fluid retention, a hypokalaemic alkalosis, and osteoporosis. A proximal myopathy, cataracts, mania, and an increased susceptibility to peptic ulcer disease may also complicate the use of the drug.

Kinetics

Absorption

Prednisolone is rapidly and completely absorbed when administered orally or rectally; the bioavailability by either route is 80–100%.

Distribution

The drug is reversibly bound in the plasma to albumin and a specific corticosteroid-binding globulin; the drug is 80–90% protein-bound at low concentrations, but only 60–70% protein-bound at higher concentrations. The V_D is 0.35–0.7 l/kg according to the dose.

Metabolism

Occurs in the liver by hydroxylation with subsequent conjugation.

Excretion

11–14% of the dose is excreted unchanged in the urine. The clearance is dose-dependent and ranges from 170–200 ml/min; the elimination half-life is 2.6–5 hours.

Special points

Prednisone and prednisolone are metabolically interchangeable; only the latter is active. The conversion of prednisone to prednisolone is rapid and extensive and occurs as a first-pass effect in the liver. Prednisolone is 4 times as potent as hydrocortisone and 6 times less potent than dexamethasone. It has been recommended that perioperative steroid cover be given:

1. to patients who have received steroid replacement therapy for 2 weeks prior to surgery or for 1 month in the year prior to surgery and
2. to patients undergoing pituitary or adrenal surgery.

Glucocorticoids antagonize the effects of anticholinesterase drugs.

Pregabalin

Uses

Pregabalin is used in the treatment of:

1. peripheral and central neuropathic pain
2. partial seizures with or without secondary generalization and
3. generalized anxiety disorder.

Chemical

The drug is a GABA analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

Presentation

As 25/50/75/100/150/200/225/300 mg capsules. Each capsule contains 35/70/8.25/11/16.5/22/24.75/33 mg of lactose monohydrate, respectively.

Main actions

Anticonvulsant, analgesic, and anxiolytic.

Mode of action

Pregabalin is structurally related to GABA, but does not interact with GABA receptors. The binding site for the drug is the alpha-2 delta subunit of voltage-gated calcium channels.

Route of administration/doses

The dose range is 150 to 600 mg/day in 2 or 3 divided doses. The initial dose is 150 mg/day, increased to 300 mg/day after 1 week with subsequent increases achieved on a weekly basis, based on individual response and tolerability. Discontinuation of treatment should be performed over at least a week. The dose needs to be reduced in patients with renal impairment.

Effects

CNS

Pregabalin has analgesic, anticonvulsant, and anxiolytic properties.

Toxicity/side effects

Weight gain may occur in diabetic patients during treatment with pregabalin, requiring dose modification of hypoglycaemic therapies. Pregabalin treatment has been associated with dizziness and somnolence. Data from controlled studies demonstrates an increased incidence of blurred vision, reduced visual acuity, and diplopia.

Kinetics

Absorption

Pregabalin is rapidly absorbed orally in the fasted state and has a bioavailability of >90% and is independent of the dose administered. The rate of absorption is decreased when the drug is given with food.

Distribution

The drug is not bound to plasma proteins; the V_D is 0.56 l/kg. Animal studies demonstrate that pregabalin crosses the placenta and is present in breast milk.

Metabolism

Pregabalin undergoes minimal metabolism in man. 0.9% of an administered dose is excreted as the major metabolite, N-methylated pregabalin.

Excretion

Approximately 98% of an administered dose is excreted unchanged in the urine. The elimination half-life is 6.3 hours. Pregabalin plasma and renal clearance are directly proportional to creatinine clearance.

Special points

Due to the lactose content of pregabalin preparations, the drug should be avoided in patients with galactose intolerance, lactase deficiency, or glucose-galactose malabsorption.

The drug is removed by haemodialysis with plasma pregabalin concentrations reduced by approximately 50% following 4 hours of haemodialysis.

Prilocaine

Uses

Prilocaine is used as a local anaesthetic.

Chemical

A secondary amide which is an amide derivative of toluidine.

Presentation

As a clear, colourless solution containing racemic prilocaine hydrochloride (S- and R-enantiomers) in concentrations of 0.5/1/2/4%. A 3% solution with 0.03 IU of felypressin per ml is also available. The pKa of prilocaine is 7.7–7.9 and is 33% unionized at a pH of 7.4. The heptane:buffer partition coefficient is 0.9.

Main action

Local anaesthetic.

Mode of action

Local anaesthetics diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels; here they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the cell membrane.

Routes of administration/doses

Prilocaine may be administered topically, by infiltration, or epidurally; the toxic dose of prilocaine is 6 mg/kg (8 mg/kg with felypressin). The maximum dose is 400 mg. The drug has a rapid onset of action and has a duration of action 1.5 times that of lidocaine.

Effects

CVS

Prilocaine has few haemodynamic effects when used in low doses, except to cause a slight increase in the systemic vascular resistance, leading to a mild increase in the blood pressure. In toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility, producing hypotension and possibly cardiovascular collapse.

RS

The drug causes bronchodilatation at subtoxic concentrations. Respiratory depression occurs in the toxic dose range.

CNS

The principle effect of prilocaine is reversible neural blockade; this leads to a characteristically biphasic effect in the central nervous system. Initially, excitation (lightheadedness, dizziness, visual and auditory disturbances, and seizure activity) occurs due to inhibition of inhibitory interneuron pathways in the cortex. With increasing doses, depression of both facilitatory and inhibitory pathways occurs, leading to central nervous system depression (drowsiness, disorientation, and coma). Local anaesthetic agents block neuromuscular transmission when administered intraneurally; it is thought that a complex of neurotransmitter, receptor, and local anaesthetic is formed, which has negligible conductance.

AS

Local anaesthetics depress contraction of the intact bowel.

Toxicity/side effects

Prilocaine is intrinsically less toxic than lidocaine. Allergic reactions to the amide-type local anaesthetic agents are extremely rare. The side effects are predominantly correlated with excessive plasma concentrations of the drug, as described above. Methaemoglobinaemia may occur if doses in excess of 600 mg are used caused by a metabolite, O-toluidine, although this condition may occur at lower doses in patients suffering from anaemia, a haemoglobinopathy, or in patients receiving therapy known to also precipitate methaemoglobinaemia (sulphonamides). Use of prilocaine for paracervical block or pudendal nerve block in obstetric patients is not recommended as this may give rise to methaemoglobinaemia in the neonate as the erythrocytes are deficient in methaemoglobin reductase.

Kinetics

Data are incomplete.

Absorption

The absorption of local anaesthetic agents is related to:

1. the site of injection (intercostal > caudal > epidural > brachial plexus > subcutaneous)
2. the dose—a linear relationship exists between the total dose and the peak blood concentrations achieved and
3. the presence of vasoconstrictors which delay absorption.

The addition of adrenaline to prilocaine solutions does not influence the rate of systemic absorption as:

1. the drug is highly lipid-soluble and therefore, uptake into fat is rapid and
2. the drug has a direct vasodilatory effect.

Distribution

Prilocaine is 55% protein-bound in the plasma, predominantly to alpha-1 acid glycoprotein; the V_D is 190–260 l.

Metabolism

Prilocaine is rapidly metabolized in the liver by amide hydrolysis, initially to O-toluidine which is in turn metabolized by hydroxylation to 4- and 6-hydroxytoludine. Some metabolism also occurs in the lungs and kidney. Excessive plasma concentrations of O-toluidine may lead to the development of methaemoglobinaemia, which responds to the administration of 1–2 mg/kg of methylene blue.

Excretion

<5% of the dose is excreted unchanged in the urine. The terminal elimination half-life is 1.6 hours.

Special points

The onset and duration of conduction blockade is related to the pKa, lipid solubility, and the extent of protein binding. A low pKa and high lipid solubility are associated with a rapid onset time; a high degree of protein binding is associated with a long duration of action. Local anaesthetic agents significantly increase the duration of action of both depolarizing and non-depolarizing relaxants.

EMLA® (Eutectic Mixture of Local Anaesthetics) is a white cream used to provide topical anaesthesia prior to venepuncture and has also been used to provide anaesthesia for split skin grafting. It contains 2.5% lidocaine and 2.5% prilocaine in an oil-water emulsion. When applied topically under an occlusive dressing, local anaesthesia is achieved after 1–2 hours and lasts for up to 5 hours. The preparation causes temporary blanching and oedema of the skin; detectable methaemoglobinaemia may also occur.

Prochlorperazine

Uses

Prochlorperazine is used in the treatment of:

1. nausea and vomiting
2. vertigo
3. psychotic states, including mania and schizophrenia, and
4. in premedication.

Chemical

A phenothiazine of the piperazine subclass.

Presentation

As tablets containing 3/5/25 mg, suppositories containing 5/25 mg, as a clear, colourless solution for injection containing 12.5 mg/ml of prochlorperazine maleate, and as a syrup containing 1 mg/ml of prochlorperazine mesilate.

Main actions

Antiemetic.

Mode of action

The antiemetic and neuroleptic effects of the drug appear to be mediated by central dopaminergic (D2) blockade, leading to an increased threshold for vomiting at the chemoreceptor trigger zone; in higher doses, prochlorperazine appears to have an inhibitory effect at the vomiting centre.

Routes of administration/doses

The adult dose is 5–20 mg 8–12-hourly and the corresponding intramuscular dose is 12.5 mg 6-hourly.

Effects

CVS

Prochlorperazine may cause orthostatic hypotension secondary to alpha-adrenergic blockade. ECG changes, including an increased QT interval, ST depression, and T and U wave changes, may also occur.

RS

The drug may cause mild respiratory depression.

CNS

Prochlorperazine has neuroleptic properties, but appears to be less soporific than perphenazine.

AS

Lower oesophageal tone is increased by the drug.

Metabolic/other

In common with other phenothiazines, prochlorperazine has anti-adrenergic, anti-inflammatory, antipruritic, anticholinergic, and antihistaminergic effects. The drug may also cause hyperprolactinaemia.

Toxicity/side effects

Prochlorperazine may cause extrapyramidal reactions, jaundice, leucopaenia, and rashes. The neuroleptic malignant syndrome (a complex of symptoms that include catatonia, cardiovascular lability, hyperthermia, and myoglobinaemia), which has a mortality in excess of 10%, has been reported in association with the use of the drug.

Kinetics

Data are incomplete.

Absorption

The drug is slowly absorbed when administered orally; the bioavailability is 0–16% by this route.

Distribution

The drug is highly protein-bound (91–99%); the V_D is 20–22 l/kg.

Metabolism

Prochlorperazine undergoes significant first-pass metabolism in the liver; its metabolic pathways include CYP3A4 and CYP2D6. Metabolism may occur by S-oxidation to a sulphoxide.

Excretion

The half-life of prochlorperazine is 6–8 hours.

Special points

Prochlorperazine is not removed by haemodialysis.

Promethazine

Uses

Promethazine is used in the treatment of:

1. nausea and vomiting (including motion sickness)
2. allergic reactions
3. pruritus and for
4. sedation in children.

Chemical

A phenothiazine.

Presentation

As 10/25 mg tablets, an elixir containing 1 mg/ml, and a clear, colourless solution for injection containing 25 mg/ml of promethazine hydrochloride.

Main actions

Antihistaminergic, sedative, and antiemetic.

Mode of action

Promethazine acts primarily as a reversible competitive antagonist at H1 histaminergic receptors; it also has some anticholinergic, antiserotonergic, and antidopaminergic activity.

Routes of administration/doses

The adult oral dose is 20–75 mg daily in divided doses; the corresponding intramuscular and intravenous dose is 25–50 mg. The drug acts within 15 minutes and has duration of action of 8–20 hours.

Effects

CVS

When normal therapeutic doses are used, promethazine has no significant cardiovascular effects. Rapid intravenous administration may cause transient hypotension.

RS

The drug causes bronchodilatation, a reduction in respiratory tract secretions, and has antitussive properties.

CNS

Promethazine is a potent sedative and anxiolytic; it also has a slight antanalgesic effect. It reduces motion sickness by suppression of vestibular end-organ receptors and by an inhibitory action at the chemoreceptor trigger zone. The drug has local anaesthetic properties.

AS

Promethazine decreases the tone of the lower oesophageal sphincter.

Toxicity/side effects

The drug exhibits predictable anticholinergic side effects and may produce extrapyramidal reactions when used in high doses. Jaundice, photosensitivity, excitatory phenomena, and gastrointestinal and haemopoietic disturbances may complicate the use of promethazine.

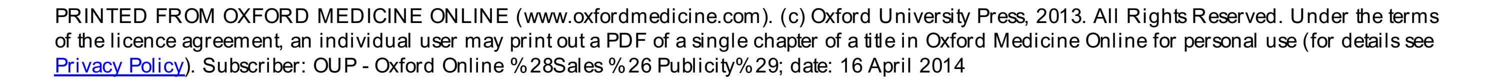
Kinetics

Absorption

Promethazine is well absorbed when administered orally, but undergoes an extensive first-pass metabolism.

Distribution

The drug is 93% protein-bound in the plasma; the V_D is 2.5 l/kg.



Metabolism

Promethazine is metabolized in the liver by sulphoxidation and N-dealkylation.

Excretion

Occurs predominantly in the urine, 2% unchanged. The clearance is 1.41 l/min and the elimination half-life is 7.5–10 hours.

Special points

The depressant effects of the drug on the central nervous system are additive with those produced by anaesthetic agents.

Promethazine is not removed by haemodialysis.

Propofol

Uses

Propofol is used:

1. for the induction and maintenance of general anaesthesia
2. for sedation during intensive care and regional anaesthesia and has been used
3. in the treatment of refractory nausea and vomiting in patients receiving chemotherapy and
4. in the treatment of status epilepticus.

Chemical

Propofol is 2,6-diisopropylphenol; a phenol derivative; molecular weight 178.27. It is a weak organic acid with a pKa of 11.

Presentation

Being highly lipid-soluble, as a white oil-in-water emulsion containing 1% or 2% w/v of propofol in soybean oil (100 mg/ml), egg lecithin (purified egg phosphatide) (12 mg/ml), benzyl alcohol (1 mg/ml) (to retard the growth of accidental microorganism inoculation), glycerol (22.5 mg/ml), and sodium hydroxide to adjust pH (7–8.5).

Main action

Hypnotic.

Mode of action

The mode of action is unclear. It potentiates the inhibitory transmitters, glycerine and GABA (via different mechanisms to those of thiobarbiturates and benzodiazepines), and may reduce Na^+ channel opening times.

Routes of administration/doses

Propofol is administered intravenously in a bolus dose of 1.5–2.5 mg/kg for induction and as an infusion of 4–12 mg/kg/hour for maintenance of anaesthesia in adults. Children require a bolus dose increase of 50% and increase of maintenance infusion by 25–50%. Patients who are elderly or unstable require dose reductions accordingly (induction 1–1.5 mg/kg, maintenance 3–6 mg/kg/hour). Co-induction of an opioid and or benzodiazepine or administration as premedication will lower the required dose of propofol further. Consciousness is lost in about 30–40 seconds with emergence occurring approximately after 10 minutes from a single dose. Plasma concentrations of 2–6 micrograms/ml and 0.5–1.5 micrograms/ml are associated with hypnosis and sedation, respectively.

Effects

CVS

Propofol produces a 15–25% decrease in blood pressure and systemic vascular resistance without a compensatory increase in heart rate; the cardiac output decreases by 20%. In fit patients, the haemodynamic response to laryngoscopy is attenuated. Vasodilatation occurs, secondary to propofol-stimulated production and release of nitric oxide. Profound bradycardia, possibly through resetting of the baroreceptor reflex, and asystole may complicate the use of the drug.

RS

Bolus administration of propofol produces apnoea of variable duration (30 to ≥60 seconds) and suppression of laryngeal reflexes. Infusion of the drug produces a decrease in tidal volume, tachypnoea, and a depressed ventilatory response to hypercarbia and hypoxia. Propofol causes bronchodilation, possibly via a direct effect on bronchial smooth muscle. The drug does not increase intrapulmonary shunting and may preserve the mechanism of hypoxic pulmonary vasoconstriction.

CNS

Propofol produces a smooth, rapid induction with rapid and clear-headed recovery. Intracranial pressure, cerebral perfusion pressure, and cerebral oxygen consumption all decrease following drug administration. Up to 10% of patients may manifest excitatory effects in the form of dystonic movements. These may be due to an imbalance between subcortical excitatory and inhibitory centres. Such movements are not accompanied by seizure activity on EEG recordings and propofol has been used in the treatment of status epilepticus. Animal models demonstrate that propofol has anticonvulsant properties. There are case reports of vivid dreams, some of a sexual nature, following propofol maintenance.

Intraocular pressure is decreased following administration of propofol in normal subjects.

AS

Propofol appears to possess intrinsic antiemetic properties which may be mediated by antagonism of dopamine D2 receptors.

GU

In animals, propofol causes a reduction in the excretion of sodium ions.

Metabolic/other

Special care should be applied in patients with disorders of fat metabolism or patients receiving total parenteral nutrition as 1 ml of 1% propofol contains 0.1 g of fat (medium chain triglycerides) with a calorific value of 1 Cal/ml. Clinically significant impairment of adrenal steroidogenesis does not occur. Propofol is a free radical scavenger.

Toxicity/side effects

Pain on injection occurs in up to 28% of subjects. The incidence may be reduced by addition of lidocaine (1 ml of 1%), cooling the drug, and the use of large veins. Addition of lidocaine in quantities greater than 20 mg lidocaine per 200 mg propofol results in emulsion instability and increases in globule size, which has been associated with reduced anaesthetic potency in animals. There are case reports of epileptiform movements, facial paraesthesiae, and bradycardia following the administration of propofol, although the incidence of allergic phenomena is low. The use of propofol appears to be safe in patients susceptible to porphyria (although urinary porphyrin concentrations may increase) and malignant hyperpyrexia. There are reports of neurological sequelae and increased mortality complicating long-term use.

Propofol infusion syndrome has been seen in both children and adults receiving prolonged propofol administration and is characterized by metabolic acidosis, rhabdomyolysis, and multi-organ failure. It is not licensed for sedation on ITU for children less than 16 years of age. The quinol metabolites may occasionally cause green discoloration of the urine and hair. Propofol should not be used in patients allergic to soya or peanuts.

Kinetics

Distribution

Propofol is 98% protein-bound in the plasma; the V_D is 4 l/kg. The distribution half-life is 1.3–4.1 minutes, resulting in a brief duration of action following bolus administration of the drug as it distributes into different compartments (alpha phase). The distribution of propofol is based on a three-compartment pharmacokinetic model which is employed in target-controlled infusion programmes.

Metabolism

Propofol is rapidly metabolized in the liver, undergoing conjugation to an inactive glucuronide (49–73%), or metabolized to a quinol which is excreted as sulphate and glucuronide conjugates of the hydroxylated metabolite via cytochrome P450. Inter-patient variability determines the ratio between the glucuronide and hydroxylated pathway. Extrahepatic metabolism probably contributes since drug clearance exceeds hepatic blood flow. Renal and hepatic disease has no clinically significant effect on the metabolism of propofol.

Excretion

The metabolites are excreted in the urine. 0.3% is excreted unchanged. The clearance is 18.8–40.3 ml/kg/min and elimination half-life is 9.3–69.3 minutes. The clearance is higher in children and decreased in the presence of renal failure. Following extended administration, its terminal elimination half-life may be prolonged together with an increasing context-sensitive half-time although under normal conditions, propofol is non-cumulative.

Special points

Propofol may increase the energy required for successful cardioversion. The drug causes shortened duration of seizure activity during electroconvulsive therapy although it does not decrease the efficacy of the treatment. Propofol is physically incompatible with atracurium. Aqueous emulsions of the drug support both bacterial and fungal growth, leading to the development of a formulation of propofol in 0.005% disodium edetate (EDTA) which provides less support for bacterial growth. Target-controlled infusion models can be used for propofol maintenance, such as ‘Marsh’ or ‘Schnider’, which use patient covariates to maintain a predetermined plasma or ‘effector site’ concentration.

Propranolol

Uses

Propranolol is used in the treatment of:

1. hypertension
2. angina
3. a variety of cardiac tachydysrhythmias
4. essential tremor and in the adjunctive management of
5. anxiety
6. thyrotoxicosis
7. hypertrophic obstructive cardiomyopathy
8. phaeochromocytoma and in the prophylaxis of
9. recurrence of myocardial infarction
10. migraine and
11. oesophageal varices.

Chemical

An aromatic amine.

Presentation

As tablets containing 10/40/80/160 mg and as a clear solution for injection containing 1 mg/ml of propranolol hydrochloride.

Main actions

Negative inotropism and chronotropism.

Mode of action

Propranolol acts by competitive antagonism of beta-1 and beta-2 adrenoceptors; it has no intrinsic sympathomimetic activity. It also exerts a membrane stabilizing effect when used in very high doses by the inhibition of sodium ion currents.

Routes of administration/doses

The adult oral dose is 30–320 mg/day in 2–3 divided doses, according to the condition requiring treatment. The corresponding dose by the intravenous route is 1–10 mg, titrated according to response.

Effects

CVS

Propranolol is negatively inotropic and chronotropic and leads to a decrease in myocardial oxygen consumption; the mechanism of the antihypertensive action of the drug remains poorly defined. Blockade of beta-2 adrenoceptors produces an increase in the peripheral vascular resistance.

RS

Propranolol causes a decrease in FEV1 by increasing airways resistance; it also attenuates the ventilatory response to hypercapnia.

CNS

The drug crosses the blood–brain barrier; its central effects may be involved in the mechanism of the antihypertensive action of the drug. Propranolol diminishes physiological tremor and decreases intraocular pressure.

GU

Propranolol decreases uterine tone, especially during pregnancy.

Metabolic/other

The drug decreases plasma renin activity and suppresses aldosterone release. Propranolol causes a decrease in the plasma free fatty acid concentration and may also cause hypoglycaemia due to blockade of gluconeogenesis. The drug increases total body sodium concentration and thus the extracellular fluid volume. Propranolol prevents the peripheral conversion of levothyroxine to triiodothyronine.

Toxicity/side effects

The side effects of propranolol are predictable manifestations of non-specific beta-adrenergic blockade. The drug may thus precipitate heart failure or heart block, exacerbate peripheral vascular disease, lead to bronchospasm, sleep disturbances, and nightmares, mask the symptoms of hypoglycaemia, and cause impaired exercise tolerance.

Kinetics

Absorption

90% of an oral dose of propranolol is absorbed; the bioavailability is 30–35% due to an extensive first-pass metabolism.

Distribution

The drug is 90–96% protein-bound in the plasma, predominantly to alpha-1 acid glycoprotein; the V_D is 3.6 l/kg.

Metabolism

Propranolol undergoes extensive hepatic metabolism by oxidative deamination and dealkylation with subsequent glucuronidation; the 4-hydroxy metabolite is active.

Excretion

Occurs via the urine; less than 1% of the dose is excreted unchanged. The clearance is 0.5–1.2 l/min and the elimination half-life is 2–4 hours. The dose should be reduced in the presence of hepatic failure; no alteration in dose is necessary in the presence of renal impairment.

Special points

Beta-adrenergic blockade should be continued throughout the perioperative period; abrupt withdrawal of propranolol may precipitate angina, ventricular dysrhythmias, myocardial infarction, and sudden death. The co-administration of propranolol and non-depolarizing relaxants may lead to a slight potentiation of the latter.

The drug is not removed by dialysis.

Protamine

Uses

Protamine is used:

1. to neutralize the anticoagulant effects of heparin and
2. to prolong the effects of insulin.

Chemical

A purified mixture of low molecular weight cationic proteins prepared from fish sperm.

Presentation

As a clear, colourless solution for injection containing 10 mg/ml of protamine sulphate.

Main actions

Neutralization of the anticoagulant effect of heparin; in high doses, protamine has a weak intrinsic anticoagulant effect.

Mode of action

Both *in vitro* and *in vivo*, the strongly basic compound protamine complexes with the strongly acidic compound, heparin, to form a stable salt—this complex is inactive. The intrinsic anticoagulant effect of the drug appears to be due to the inhibition of the formation and activity of thromboplastin.

Routes of administration/doses

Protamine is administered by slow intravenous injection; the dose should be adjusted according to the amount of heparin that is to be neutralized, the time that has elapsed since the administration of heparin and the activated coagulation time (ACT). 1 mg of protamine will neutralize 100 units of heparin. A maximum adult dose of 50 mg of the drug should be administered in any 10-minute period.

Effects

CVS

Protamine is a myocardial depressant and may cause bradycardia and hypotension secondary to complement activation and leukotriene release. The pulmonary artery pressure may increase, leading to an impairment of right ventricular output.

Toxicity/side effects

Rapid intravenous administration of protamine may be complicated by acute hypotension, bradycardia, dyspnoea, and flushing. Anaphylactoid reactions may also occur; antibodies to human protamine often develop in vasectomized males and may predispose to hypersensitivity phenomena.

Kinetics

Data are incomplete.

Metabolism

The metabolic fate of the protamine heparin complex has not been well elucidated; it may undergo partial degradation, thereby freeing heparin.

Prothrombin complex

Uses

Prothrombin complex is used in the treatment and prophylaxis of bleeding resulting from congenital or acquired deficiencies of prothrombin complex coagulation factors.

Chemical

Human plasma-derived prothrombin complex coagulation factors (II, VII, IX, and X) together with Protein C and Protein S.

Presentation

As a powder in vials containing 250 or 500 IU together with a solvent for intravenous injection. Following reconstitution, the following approximate concentrations of each component are present:

- factor II—20 to 48 IU/ml
- factor VII—10 to 25 IU/ml
- factor IX—30 to 31 IU/ml
- factor X—22 to 60 IU/ml
- Protein C—15 to 45 IU/ml
- Protein S—12 to 38 IU/ml.

The total protein content following reconstitution is 6–15 mg/ml. The following substances are also present: heparin, human antithrombin III, human albumin, sodium chloride, sodium citrate, and hydrochloric acid or sodium hydroxide for pH adjustment. The sodium content of reconstituted prothrombin complex is up to 343 mg per 100 ml.

Main actions

Neutralization of the anticoagulant effect resulting from deficiency in factors II, VII, IX, and X.

Mode of action

Increased plasma levels of factors II, VII, IX, and X.

Routes of administration/doses

Prothrombin complex is administered intravenously. Advice regarding the dose and administration frequency should be sought from a haematologist prior to administration.

Toxicity/side effects

There is a risk of subsequent thrombosis and/or disseminated intravascular coagulation with repeated dosing. There are very rare reports of allergic reactions during or following administration. Development of antibodies to any of the coagulation factors may occur very rarely.

Kinetics

Data are incomplete.

Distribution

Distribution of prothrombin complex is identical to endogenous coagulation factors.

Metabolism

Plasma half-life of each component of prothrombin complex is as follows:

- factor II—60 hours
- factor VII—4 hours
- factor IX—17 hours
- factor X—31 hours
- Protein C—47 hours
- Protein S—49 hours.

Factors IX and X and Protein C and S exhibit two-compartment model pharmacokinetics. Metabolic pathways involved in prothrombin complex metabolism are identical to those involved in endogenous factor/protein breakdown.







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Susan Smith, Edward Scarth, and Martin Sasada

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Ranitidine

Uses

Ranitidine is used in the treatment of:

1. peptic ulcer disease
2. reflux oesophagitis
3. the Zollinger–Ellison syndrome and
4. for the prevention of stress ulceration in critically ill patients and
5. prior to general anaesthesia in patients at risk of acid aspiration, especially during pregnancy and labour.

Chemical

A furan derivative.

Presentation

As a clear solution for intravenous or intramuscular injection containing 25 mg/ml, as 150/300 mg tablets, and as a syrup containing 15 mg/ml of ranitidine hydrochloride.

Main actions

Inhibition of gastric acid secretion.

Mode of action

Ranitidine acts via competitive blockade of histaminergic H2 receptors. Histamine appears to be necessary to potentiate the action of gastrin and acetylcholine on the gastric parietal cell as well as acting directly as a secretagogue.

Routes of administration/doses

Ranitidine may be administered by slow intravenous or intramuscular injection, the dose being 50 mg 6–8-hourly. The oral dose is 150 mg twice daily.

Effects

CVS

No effect is seen with normal clinical dosages.

RS

The drug has no effect on respiratory parameters.

AS

Ranitidine profoundly inhibits gastric acid secretion, reducing the volume, and hydrogen ion and pepsin content. The drug has a longer duration of antisecretory activity than cimetidine. Ranitidine has been reported to cause a dose-related increase in lower oesophageal sphincter tone.

Metabolic/other

Ranitidine does not show the anti-androgenic, antidopaminergic, or effects on cytochrome P450-mediated metabolism that are associated with cimetidine. The drug crosses the placenta, but no adverse effects on fetal well-being have been demonstrated.

Toxicity/side effects

Reversible abnormalities of liver function tests, rashes, and anaphylactoid reactions have been reported following the use of ranitidine. Reversible confusion, thrombocytopaenia, and leucopaenia occur rarely after administration of the drug.

Kinetics

Absorption

Ranitidine has an oral bioavailability of 50–60%.

Distribution

The drug is approximately 15% protein-bound in the plasma; the V_D is 1.2–1.8 l/kg.

Metabolism

A small fraction of the drug is metabolized by oxidation and methylation.

Excretion

Ranitidine is predominantly excreted unchanged by the kidney. The clearance is 10 ml/min/kg and the elimination half-life is 1.6–2.5 hours.

Special points

A reduced dosage of the drug should be used in patients with renal failure; the drug is removed by haemodialysis.

Ranitidine may be associated with an increase in nosocomial pneumonia in ventilated, critically ill patients.

Remifentanil

Uses

Remifentanil is used:

1. to provide the analgesic component in general anaesthesia
2. to provide analgesia/sedation in intensive care
3. to provide analgesia during labour when regional anaesthesia is not in use
4. to provide analgesia/sedation during 'awake' fibreoptic intubation.

Chemical

A synthetic phenylpiperidine derivative of fentanyl.

Presentation

As a white lyophilized powder to be reconstituted before use containing remifentanil hydrochloride in a glycine buffer in 1/2/5 mg vials for dilution prior to infusion. It has a pKa of 7.1 and is 68% unionized at a pH of 7.4.

Main actions

Analgesia and respiratory depression.

Mode of action

Remifentanil is a pure mu-agonist (or MOP agonist); the mu-opioid receptor (MOP receptor) appears to be specifically involved in the mediation of analgesia. Opioids appear to exert their effects by interacting with pre-synaptic Gi-protein receptors, leading to hyperpolarization of the cell membrane by increasing K^+ conductance. Inhibition of adenylate cyclase, leading to reduced production of cyclic adenosine monophosphate and closure of voltage-sensitive calcium channels, also occurs. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routes of administration/doses

Remifentanil is licensed for intravenous administration only. The drug may be given by slow bolus injection of 1 micrograms/kg over at least 30 seconds or by target controlled infusion with an approved infusion device incorporating, e.g. the 'Minto' pharmacokinetic model with covariates for age and lean body mass. A manual infusion technique may also be used, titrated to response. The drug may be infused at a rate of 0.0125–1 micrograms/kg/min, depending on the level of sedation and analgesia required. The peak effect of the drug occurs within 1–3 minutes. The offset is rapid and predictable, even after prolonged infusion, typically occurring within 5–10 minutes of discontinuation of the infusion. Administration of remifentanil reduces the amount of hypnotic/volatile agent required to maintain anaesthesia.

Effects

CVS

Remifentanil decreases mean arterial pressure and heart rate by 20%. Myocardial contractility and cardiac output may also decrease.

RS

Remifentanil is a potent respiratory depressant, causing a decrease in both the respiratory rate and tidal volume; it also diminishes the ventilatory response to hypoxia and

hypercarbia. Chest wall rigidity (the 'wooden chest' phenomenon) may occur after the administration of remifentanil—this may be an effect of the drug on mu-receptors located on GABA-ergic interneurons. The drug does not cause histamine release.

CNS

Remifentanil has a centrally mediated vagal activity. It has an analgesic potency similar to fentanyl and possesses minimal hypnotic or sedative activity. It produces EEG effects similar to those of other opioids—high-amplitude, low-frequency activity. Miosis is produced as a result of stimulation of the Edinger–Westphal nucleus.

AS

The drug decreases gastrointestinal motility and there is a relatively low incidence of nausea and vomiting associated with its use.

Toxicity/side effects

Respiratory depression, bradycardia, nausea, and vomiting may all complicate the use of remifentanil. Because of its short duration of action, post-operative discomfort may be pronounced if remifentanil is used as a sole analgesic agent perioperatively.

Kinetics

Distribution

Remifentanil is 70% bound to plasma proteins, two-thirds to alpha-1 acid glycoprotein. The drug has a low lipid solubility compared to other mu-opioids, with a low volume of distribution of 0.1 l/kg and distributes into peripheral tissues with a volume of distribution at steady state, VD_{SS}, of 0.25–0.4 l/kg. Remifentanil crosses the placenta and may cause respiratory depression in the neonate. In children aged 1 to 12 years, the volume of distribution decreases with increasing age. The V_D in neonates is twice that of adults.

Metabolism

Remifentanil undergoes rapid ester hydrolysis by non-specific plasma and tissue esterases to a carboxylic acid derivative, remifentanil acid, which is 4600-fold less potent than remifentanil. The context-sensitive half-time of remifentanil, 3–5 minutes, is fixed due to the quantity of the above esterases and does not increase with the duration of the infusion, unlike other opioids. The drug is not metabolized by plasma cholinesterases and is unaffected by its deficiency or by the administration of anticholinesterase drugs.

Excretion

The clearance of remifentanil is 4.2–5 l/min and independent of renal and hepatic function. The elimination half-life is 5–14 minutes and is unaltered with renal and hepatic dysfunction. Approximately 95% of an administered dose is excreted in the urine as remifentanil acid which has an elimination half-life of 1.5–2 hours. In children aged 1 to 12 years, the clearance of remifentanil decreases with increasing age. The clearance in neonates is twice that of adults although the elimination half-life is approximately the same. The pharmacokinetics of remifentanil acid are similar in children compared to those seen in adults.

Special points

The clearance of the metabolite, remifentanil acid, is prolonged in patients with renal impairment and may increase to 268 hours. The concentration of the metabolite may increase by 100-fold in intensive care patients with moderate or severe renal impairment at steady state, although there is no evidence that clinically significant mu-opioid effects are seen, even following remifentanil infusions lasting 3 days.

Intravenous lines must be flushed at the end of the infusion due to the risk of respiratory depression by the residual drug in the line dead space.

There is no evidence that remifentanil is extracted during renal replacement therapy.

Remifentanil acid is extracted during haemodialysis by 25–35%.

Patients with hepatic impairment are more sensitive to the respiratory depressant effects of remifentanil.

Rivaroxaban

Uses

Rivaroxaban is used for the prevention of venous thromboembolism in patients undergoing elective knee and hip replacement surgery.

Chemical

An oxazolidinone derivative.

Presentation

As 10 mg tablets containing rivaroxaban. Each tablet also contains 27.9 mg lactose monohydrate.

Main actions

Direct factor Xa inhibitor.

Mode of action

Rivaroxaban directly inhibits factor Xa in a dose-dependent manner, leading to interruption of both the intrinsic and extrinsic coagulation pathways. The drug does not inhibit thrombin and has no effect on platelet function.

Route of administration/doses

The drug is administered orally at a dose of 10 mg. The first dose should be given 6 to 10 hours after surgery. Treatment should continue for 5 weeks following hip surgery and 2 weeks following knee surgery. No dose adjustment is required for patients with mild or moderately impaired renal function. The drug should be used with caution in patients with severe renal impairment.

Effects

Metabolic/other

The main effect of the drug is its anticoagulation effect. Rivaroxaban does not affect platelet function.

Toxicity/side effects

Excessive bleeding is the most commonly reported side effect. The use of neuroaxial blocks in patients receiving the drug must be carefully considered and the timing of block/catheter insertion/removal and commencement/withholding/discontinuation of rivaroxaban must be appropriately timed to minimize the risk of spinal/epidural haematoma formation. It is recommended that following a dose of rivaroxaban, an epidural catheter should not be removed before 18 hours has elapsed and any subsequent dose to be delayed by a further 6 hours following catheter removal.

Kinetics

Absorption

Rivaroxaban is rapidly absorbed following oral administration with C_{max} occurring within 2–4 hours of ingestion. The bioavailability of the drug is 80–100%.

Distribution

The drug is 92–95% protein-bound; the V_D is approximately 50 l.

Metabolism

Two-thirds of an administered dose undergoes oxidative degradation and hydrolysis via CYP450 3A4, CYP450 2J2, and CYP-independent mechanisms. The morpholinone moiety and amide bonds are the main metabolic targets.

Excretion

Following hepatic metabolism, 50% of the metabolic products of the drug are renally excreted whilst the remaining 50% are excreted in the faeces. Unchanged drug is excreted renally. The terminal elimination half-life of a 1 mg dose is 4.5 hours, increasing to 7–11 hours following a 10 mg dose due to absorption rate-limited elimination. The systemic clearance is approximately 10 l/hour.

Special points

In vitro studies demonstrate that the drug is a substrate of the transporter proteins, P-glycoprotein and BCRP (breast cancer resistance protein).

Drug plasma levels may be reduced when rivaroxaban is administered to patients receiving CYP450 3A4 inducers such as rifampicin, phenytoin, carbamazepine, and St John's Wort.

Drug plasma levels may increase when rivaroxaban is administered to patients receiving CYP450 3A4 and P-glycoprotein inhibitors such as ketoconazole, itraconazole, voriconazole, and HIV protease inhibitors.

There is no antidote currently available for rivaroxaban.

The drug is unlikely to be removed by haemodialysis due to high plasma protein binding.

Rocuronium

Uses

Rocuronium is used:

1. to facilitate tracheal intubation during routine and modified rapid sequence induction
2. for controlled ventilation.

Chemical

An aminosteroid which is structurally related to vecuronium.

Presentation

As a clear, colourless solution containing 10 mg/ml of rocuronium bromide. The drug is available in 5 and 10 mg ampoules.

Main action

Competitive neuromuscular blockade.

Mode of action

Rocuronium acts by competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction; it also has some pre-junctional activity.

Route of administration/doses

Rocuronium is administered intravenously; the normal intubating dose is 0.6 mg/kg with subsequent doses of 0.15 mg/kg. This intubating dose equates to twice the ED_{90} for rocuronium (ED_{90} = 0.3 mg/kg) and results in 'excellent' intubating conditions in 80% of cases within 60 seconds. A dose of 1 mg/kg is recommended when rocuronium is used during modified rapid sequence induction, resulting in intubating conditions within 60 seconds in 93–96%. The increased speed of onset relates to the low potency of rocuronium. As a result of giving an increased dose (increased number of drug molecules), the concentration gradient at the neuromuscular junction is increased, leading to faster diffusion of drug molecules and reduction in drug onset time. The duration of action relates to the dose given and as a result, the usual recovery index of 8–17 minutes with a normal intubating dose is increased to nearly an hour when 1.0 mg/kg is used. The drug may also be infused at a rate of 300–600 micrograms/kg/hour. The drug is non-cumulative with repeated administration.

Effects

CVS

Rocuronium has minimal cardiovascular effects; with large doses, a mild vagolytic effect leads to a slight (9%) increase in heart rate and an increase in mean arterial pressure of up to 16%.

RS

Neuromuscular blockade leads to apnoea. Rocuronium causes an insignificant release of histamine; bronchospasm is extremely uncommon.

Toxicity/side effects

There have been very rare reports of fatal anaphylactoid reactions with the administration of rocuronium. Cross-sensitivity may exist with other aminosteroid compounds (vecuronium, pancuronium). Pain on injection occurs in 16% of subjects when rocuronium is used in combination with propofol compared with 0.5% of subjects when thiopental is used.

Kinetics

Distribution

The drug is 30% protein-bound in the plasma; the V_D is 0.27 l/kg.

Metabolism

No metabolites of rocuronium have been found in plasma or urine.

Excretion

Rocuronium is excreted primarily by hepatic uptake and hepatobiliary excretion. 30–40% of the dose is excreted unchanged in the bile, 13–31% in the urine. After administration of a bolus dose, the plasma concentration time course runs in three exponential phases. In adults, the mean elimination half-life is 73 (66–80) minutes with a plasma clearance of 3.7 (3.5–3.9) ml/kg/min. The pharmacokinetics of rocuronium is not significantly altered in the presence of renal failure. The mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min in the presence of hepatic dysfunction; the duration of action is correspondingly increased.

Special points

The duration of action of rocuronium, in common with other non-depolarizing relaxants, may be prolonged by hypokalaemia, hypocalcaemia, hypothermia, hypermagnesaemia, hypoproteinaemia, dehydration, acidosis, and hypercapnia. The following drugs, when co-administered with non-depolarizing relaxants, increase the effect of the latter: volatile and induction agents, fentanyl, suxamethonium, diuretics, lithium, calcium antagonists, alpha- and beta-adrenergic antagonists, protamine, metronidazole, and the aminoglycoside antibiotics.

Rocuronium is physically incompatible with thiopental, methohexital, dexamethasone, erythromycin, trimethoprim, vancomycin, and diazepam. In animal studies, rocuronium does not appear to be a triggering factor for malignant hyperpyrexia.

Rocuronium causes significantly less rise in intraocular pressure compared with suxamethonium.

Reversal of neuromuscular blocking activity by rocuronium may be achieved using neostigmine (in combination with glycopyrronium bromide), but only after four twitches have returned on the train-of-four count. The gamma-cyclodextrin, sugammadex, may be used to reverse rocuronium-induced neuromuscular blockade by encapsulating rocuronium molecules within the plasma, thereby creating a concentration gradient favouring the

movement of remaining rocuronium molecules from the neuromuscular junction back into the plasma.

Ropivacaine

Uses

Ropivacaine is used as a local anaesthetic.

Chemical

An amino amide which is member of the pipecoloxylidide group of local anaesthetics.

Presentation

As a clear, colourless solution containing racemic ropivacaine hydrochloride monohydrate (S- and R-enantiomers) in concentrations of 0.2/0.75/1.0% equivalent to 2.0 mg, 7.5 mg, and 10 mg/ml, respectively, of ropivacaine hydrochloride. A pure S-ropivacaine preparation is also available. It is not available in combination with a vasoconstrictor as this does not alter its tissue uptake or duration of action. The pKa of ropivacaine is 8.1 and it is 15% unionized at a pH of 7.4. The heptane: buffer partition coefficient is 2.9. The preparation also contains sodium hydroxide equivalent to 3.7 mg of sodium per ml.

Main action

Local anaesthetic.

Mode of action

Local anaesthetics diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane sodium ion channels; here they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the cell membrane.

S-ropivacaine is more potent and less cardiotoxic than R-ropivacaine.



Routes of administration/doses

Ropivacaine may be administered topically, by infiltration, or epidurally; the drug is not currently intended for use in spinal anaesthesia. The maximum recommended dose of ropivacaine is 3 mg/kg. Sensory blockade is similar in time course to that produced by bupivacaine; motor blockade is slower in onset and shorter in duration than that after an equivalent dose of bupivacaine. Alkalinization of 0.75% ropivacaine significantly increases the duration of action of epidural blockade.

Effects

CVS

Ropivacaine is less cardiotoxic than bupivacaine; in toxic concentrations, the drug decreases the peripheral vascular resistance and myocardial contractility, producing hypotension and possibly cardiovascular collapse. Ropivacaine has a biphasic vascular effect, causing vasoconstriction at low, but not at high, concentrations.

CNS

The principle effect of ropivacaine is reversible neural blockade; this leads to a characteristically biphasic effect in the central nervous system.

Initially, excitation (lightheadedness, dizziness, visual and auditory disturbances, and seizure activity) occurs due to inhibition of inhibitory interneuron pathways in the cortex. With increasing doses, depression of both facilitatory and inhibitory pathways occurs, leading to central nervous system depression (drowsiness, disorientation, and coma). Local anaesthetic agents block neuromuscular transmission when administered intraneurally; it is thought that a complex of neurotransmitter, receptor, and local anaesthetic is formed, which has negligible conductance.

GU

Ropivacaine does not compromise uteroplacental circulation.

Toxicity/side effects

Allergic reactions to the amide-type local anaesthetic agents are extremely rare. The side effects are predominantly correlated with excessive plasma concentrations of the drug, as described above.

Kinetics

Absorption

The absorption of local anaesthetic agents is related to:

1. the site of injection (intercostal > caudal > epidural > brachial plexus > subcutaneous)
2. the dose—a linear relationship exists between the total dose and the peak blood concentrations achieved and
3. the presence of vasoconstrictors which delay absorption.

Distribution

Ropivacaine is 94% protein-bound in the plasma, predominantly to alpha-1 acid glycoprotein; the V_D is 52–66 l. The drug demonstrates a biphasic absorption profile from the epidural space with half-lives of 14 minutes and 4 hours in adults.

Metabolism

Ropivacaine is metabolized in the liver by aromatic hydroxylation via cytochrome CYP1A2 to 3-hydroxy-ropivacaine, the major metabolite, 4-hydroxy-ropivacaine and 4-hydroxy-dealkylated-ropivacaine. Co-administration of a CYP1A2 inhibitor (e.g. fluvoxamine, enoxacin) may reduce plasma clearance of the drug by up to 77% *in vitro*. The isoenzyme CYP3A4 is also involved in the metabolism of ropivacaine as administration of a CYP3A4 inhibitor (e.g. fluconazole) reduces the plasma clearance of the drug by 15% *in vitro*, although this is unlikely to cause a clinically significant effect. Ropivacaine has an intermediate hepatic extraction ratio of approximately 0.4. There is no evidence of *in vivo* racemization of ropivacaine.

Excretion

The clearance is 0.44–0.82 l/min and the terminal elimination half-life is 59–173 minutes. 86% of the dose is excreted in the urine, 1% unchanged. 37% of 3-hydroxy-ropivacaine is excreted in the urine, predominantly conjugated. The elimination half-life is longer after epidural (4.2 hours) than after intravenous administration due to the biphasic absorption from the former, as described above.

Special points

The onset and duration of conduction blockade is related to the pKa, lipid solubility, and the extent of protein binding. A low pKa and high lipid solubility are associated with a rapid onset time; a high degree of protein binding is associated with a long duration of action. Local anaesthetic agents significantly increase the duration of action of both depolarizing and non-depolarizing relaxants.







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Salbutamol

Uses

Salbutamol is used in the treatment of:

1. asthma
2. chronic obstructive airways disease and
3. uncomplicated preterm labour.

Chemical

A synthetic sympathomimetic amine.

Presentation

As 2/4/8 mg tablets, a syrup containing 0.4/2.5 mg/ml, an aerosol delivering 100 micrograms/puff, a dry powder for inhalation in capsules containing 200/400 micrograms, a solution for nebulization containing 2.5/5 mg/ml, and as a clear, colourless solution for injection containing 1 mg/ml of salbutamol sulphate.

Main actions

Bronchodilatation and uterine relaxation.

Mode of action

Salbutamol is a beta-adrenergic agonist (with a more pronounced effect at beta-2 than beta-1 receptors) that acts by stimulation of membrane-bound adenyl cyclase in the presence of magnesium ions to increase intracellular cAMP concentrations. It also directly inhibits antigen-induced release of histamine and slow-releasing substance of anaphylaxis from mast cells.

Routes of administration/doses

The adult oral dose is 2–4 mg 6–8-hourly. One or two metered puffs of 200–400 micrograms of the powder may be inhaled 6–8-hourly. 2.5–5 mg of the nebulized solution may similarly be inhaled 6-hourly. The drug may also be administered subcutaneously or intramuscularly in a dose of 0.5 mg 4-hourly. Salbutamol should be administered intravenously as an infusion diluted in glucose or saline at a rate not exceeding 0.5 micrograms/kg/min. Bronchodilatation is observed 5–15 minutes after inhalation and 30 minutes after ingestion of the drug and lasts for up to 4 hours.

Effects

CVS

In high doses, the beta-1 actions of the drug lead to positive inotropic and chronotropic effect. At lower doses, the beta-2 effects predominate and cause a decrease in the peripheral vascular resistance, leading to a decrease in the diastolic blood pressure of 10–20 mmHg.

RS

Bronchodilatation, leading to an increased PEFR and FEV1, occurs after the administration of salbutamol. This is additive to the bronchodilatation produced by phosphodiesterase inhibitors. The drug interferes with the mechanism of hypoxic pulmonary vasoconstriction; an adequate inspired oxygen concentration should be ensured

when the drug is used.

GU

Salbutamol decreases the tone of the gravid uterus; 10% of an administered dose crosses the placenta and may lead to tachycardia in the fetus.

Metabolic/other

Salbutamol may decrease the plasma potassium concentration by causing a shift of the ion into cells. It may also cause an increase in the plasma concentrations of free fatty acids and glucose; insulin release is therefore stimulated.

Toxicity/side effects

Anxiety, insomnia, tremor (with no attendant change in motor strength), sweating, palpitations, ketosis, hypokalaemia, postural hypotension, and nausea and vomiting may occur following the use of the drug.

Kinetics

Data are incomplete.

Absorption

10% of the dose administered by inhalation reaches the bronchial tree, the remainder being swallowed.

Distribution

Salbutamol is 8–64% protein-bound in the plasma; the V_D is 156 l.

Metabolism

Salbutamol undergoes a significant first-pass metabolism in the liver; the major metabolite is salbutamol 4-O-sulphate.

Excretion

30% of the dose is excreted unchanged in the urine, the remainder in faeces, and as the sulphate derivative in the urine. The clearance is 28 l/hour and the elimination half-life is 2.7–5 hours.

Special points

Salbutamol appears to potentiate non-depolarizing muscle relaxants.

Sevoflurane

Uses

Sevoflurane is used for the induction and maintenance of general anaesthesia.

Chemical

A polyfluorinated isopropyl methyl ether.

Presentation

As a clear, colourless liquid which is non-flammable; the commercial preparation contains no additives or stabilizers and is supplied in amber coloured bottles. The molecular weight of sevoflurane is 200, the boiling point is 58.6°C, and the saturated vapour pressure is 22.7 kPa at 20°C. The MAC of sevoflurane is age-dependent and ranges from 1.4 in elderly patients to 3.3 in neonates (0.7 to 2.0 in the presence of 65% nitrous oxide), the blood/gas partition coefficient is 0.63 to 0.69, and the fat/blood partition coefficient is 52. The oil:gas partition coefficient is 47 to 54. Degradation of sevoflurane may occur by two pathways in the presence of warm, dessicated alkaline CO_2 absorbants (KOH > NaOH) at low fresh gas flows. The first pathway results in the loss of hydrogen fluoride with the production of pentafluoroisopropenyl fluoromethyl ether (PIFE or ‘compound A’) and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether (PMFE or ‘compound B’). The second pathway results in the production of hexafluoroisopropanol (HFIP) and formaldehyde. The latter may further degrade into formate and methanol. Formate can contribute to carbon monoxide production whilst methanol may react with compound A to form compound B. Compound B may undergo further loss of hydrogen fluoride to produce trace amounts of compounds C, D, and E.

Main action

General anaesthesia (reversible loss of both awareness and recall of noxious stimuli).

Mode of action

The mechanism of general anaesthesia remains to be fully elucidated. General anaesthetics appear to disrupt synaptic transmission (especially in the area of the ventrobasal thalamus). This mechanism may include potentiation of the GABA and glycine receptors and the antagonism at NMDA receptors. Their mode of action at the molecular level appears to involve the expansion of hydrophobic regions in the neuronal membrane, either within the lipid phase or within hydrophobic sites in cell membranes.

Routes of administration/doses

Sevoflurane is administered by inhalation; the agent has a pleasant, non-irritant odour. The concentration used for induction of anaesthesia is quoted as 5–8%. Maintenance of anaesthesia is usually achieved using between 0.5 and 3%.

Effects

CVS

Sevoflurane causes a dose-related decrease in myocardial contractility and mean arterial pressure; systolic pressure decreases to a greater degree than diastolic pressure.

The drug does not affect the heart rate and myocardial sensitization to catecholamines does not occur. The drug does not appear to cause the 'coronary steal' phenomenon in man.

RS

Sevoflurane is a respiratory depressant, causing dose-dependent decreases in tidal volume and an increase in respiratory rate. The drug depresses the ventilatory response to CO_2 and inhibits hypoxic pulmonary vasoconstriction. Sevoflurane appears to relax bronchial smooth muscle constricted by histamine or acetylcholine.

CNS

The principal effect of sevoflurane is general anaesthesia. The drug causes cerebral vasodilatation, leading to an increase in cerebral blood flow; cerebral metabolic rate is decreased. As with other volatile anaesthetic agents, sevoflurane may increase intracranial pressure in a dose-related manner. Sevoflurane use is not associated with epileptiform activity.

GU

Sevoflurane reduces renal blood flow and leads to an increase in fluoride ion concentrations (12–90 μmol/l in anaesthesia lasting 1 to 6 hours, respectively). There is no evidence that sevoflurane causes gross changes in human renal function. The drug causes uterine relaxation.

Metabolic/other

In animal models, the drug decreases liver synthesis of fibrinogen, transferrin, and albumin.

Toxicity/side effects

Sevoflurane may cause post-operative nausea and vomiting.

It is a trigger agent for the development of malignant hyperthermia. There are no reports of renal toxicity occurring in patients who have received the drug. Rapid emergence in paediatric patients may lead to agitation in approximately 25% of cases. Paediatric patients with Down's syndrome receiving sevoflurane for inhalational induction may develop a bradycardia in up to 52% of cases.

Kinetics

Absorption

The major factors affecting the uptake of volatile anaesthetic agents are solubility, cardiac output, and the concentration gradient between the alveoli and venous blood. Due to the low blood/gas partition coefficient of sevoflurane, it is exceptionally insoluble in blood; alveolar concentration, therefore, reaches inspired concentration very rapidly (fast wash-in rate), resulting in a rapid induction of (and emergence from) anaesthesia. An increase in cardiac output increases the rate of alveolar uptake and slows the induction of anaesthesia. The concentration gradient between the alveoli and venous blood approaches zero at equilibrium; a large concentration gradient favours the onset of anaesthesia.

Distribution

The drug is initially distributed to organs with a high blood flow (brain, heart, liver, kidney) and later to less well-perfused organs (muscle, fat, bone).

Metabolism

Sevoflurane is metabolized by the process of defluorination via CYP450 2El, producing HFIP, inorganic fluoride, and CO_2. HFIP is rapidly conjugated with glucuronic acid and eliminated in the urine. Approximately 3–5% of an administered dose is metabolized. CYP450 2El may be induced by chronic exposure to ethanol and isoniazid. It is not induced by exposure to barbiturates. Fluoride concentrations may increase significantly in the presence of increased CYP 2El activity although there are no reports from clinical trials regarding fluoride toxicity.

Excretion

Excretion is via the lungs, predominantly unchanged. Elimination of sevoflurane is rapid, again due to its low solubility, resulting in a fast wash-out rate. HFIP peak excretion occurs within 12 hours; the elimination half-life is 55 hours. Fluoride ion concentrations peak within 2 hours at the end of anaesthesia; the half-life is 15–23 hours.

Special points

Sevoflurane potentiates the action of co-administered depolarizing and non-depolarizing muscle relaxants to a greater extent than either halothane or enflurane.

As with other volatile anaesthetic agents, the co-administration of N_2O, benzodiazepines, or opioids lowers the MAC of sevoflurane.

Sodium bicarbonate

Uses

Sodium bicarbonate is used:

1. for the correction of profound metabolic acidosis, especially that complicating cardiac arrest
2. for the alkalinization of urine and
3. as an antacid.

Chemical

An inorganic salt.

Presentation

As 300 mg tablets and as a clear, colourless sterile solution containing 1.26/4.2/8.4% w/v sodium bicarbonate in an aqueous solution. The 8.4% solution contains 1 mmol/ml of sodium and bicarbonate ions and has a calculated osmolarity of 2000 mOsm/l.

Mode of action

The compound freely dissociates to yield bicarbonate ions which represent the predominant extracellular buffer system. Each gram of sodium bicarbonate will neutralize 12 mEq of hydrogen ions.

Routes of administration/doses

The adult oral dose for the relief of dyspepsia is 600–1800 mg as required. For the alkalinization of urine, an oral dose of 3 g is administered every 2 hours until the pH of the urine is 7.

When administered intravenously for the treatment of profound metabolic acidosis, the dose required to restore the pH to normal is usually calculated from the formula:

Dose (mmol) = {base deficit (mEq/l) × body weight (kg)}/3

Half this amount is administered before the acid-base status is reassessed.

Effects

CVS

Overenthusiastic correction of an acidosis will result in a metabolic alkalosis, which may result in myocardial dysfunction and peripheral tissue hypoxia due to a shift in the oxygen dissociation curve to the left.

RS

Metabolic alkalosis diminishes pulmonary ventilation by an effect on the respiratory centre.

CNS

The major clinical effect of metabolic alkalosis is excitability of the central nervous system, manifested as nervousness, convulsions, muscle weakness, and tetany.

AS

Oral administration of the drug results in the release of carbon dioxide with subsequent belching.

Metabolic/other

Hypernatraemia, hyperkalaemia, and hypocalcaemia may all result from the intravenous administration of sodium bicarbonate.

Toxicity/side effects

Hypernatraemia and hyperosmolar syndromes may complicate the use of sodium bicarbonate. The compound is highly irritant to tissues when extravasated and may cause skin necrosis and sloughing.

Kinetics

Data are incomplete.

Metabolism

Bicarbonate ions react with hydrogen ions to yield carbon dioxide and water.

Excretion

Occurs via renal excretion of bicarbonate and exhalation of carbon dioxide.

Special points

Sodium bicarbonate is physically incompatible with calcium salts (which it precipitates) and may cause inactivation of co-administered adrenaline, isoprenaline, and suxamethonium.

The use of sodium bicarbonate should be avoided in patients with renal, hepatic, or heart failure due to its high sodium content.

Hypertonic preparations of sodium bicarbonate appear to lower intracranial pressure in a manner similar to hypertonic saline.

Sodium chloride

Uses

Sodium chloride is used:

1. to provide maintenance fluid and extracellular fluid replacement
2. to replace sodium and chloride ions under circumstances of reduced intake or excessive loss
3. in the management of hyperosmolar diabetic coma
4. as a priming fluid for haemodialysis and cardiopulmonary bypass machines
5. for rehydration of neonates and infants (0.45% solutions)
6. in the management of severe salt depletion (1.8% solutions)
7. for the dilution of drugs
8. for interspinous ligament injection in the treatment of chronic neck and back pain (10% solutions) and
9. in the management of raised intracranial pressure (5% solution).

Chemical

An inorganic salt.

Presentation

As clear, colourless, sterile 0.45/0.9/1.8/5% solutions in bags of various capacities. The 0.9% solution contains 154 mmol of both sodium and chloride ions per litre. The pH ranges from 4.5–7; they contain no preservative or antimicrobial agents.

Main action

Volume expansion.

Routes of administration/doses

Hypertonic saline solutions should be administered via a central venous line.

Effects

CVS

The haemodynamic effects of sodium chloride are proportional to the prevailing circulating volume and are short-lived.

GU

Renal perfusion is temporarily restored towards normal in hypovolaemic patients transfused with the crystalloid.

Toxicity/side effects

The predominant hazard is that of overtransfusion, leading to hypernatraemia or pulmonary oedema. A hyperchloraemic metabolic acidosis may result from repeated administration of sodium chloride.

Kinetics

Absorption

Sodium chloride is rapidly and completely absorbed when administered orally.

Distribution

0.9% solution is isotonic with extracellular fluid; it is initially distributed into the intravascular compartment where it remains for approximately 30 minutes before being distributed uniformly throughout the extracellular space.

Excretion

In the urine.

Sodium nitroprusside

Uses

Sodium nitroprusside is used in the management of:

1. hypertensive crises
2. aortic dissection prior to surgery
3. left ventricular failure and
4. to produce hypotension during surgery.

Chemical

An inorganic complex.

Presentation

As an intravenous solution 10 mg/ml of sodium nitroprusside for dilution prior to infusion; it must be protected from light.

Main actions

Vasodilation and hypotension.

Mode of action

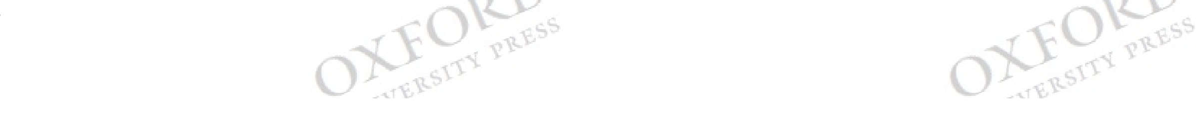
Sodium nitroprusside dilates both resistance and capacitance vessels by a direct action on vascular smooth muscle. It appears to act by interacting with sulphydryl groups in the smooth muscle cell membrane, thereby stabilizing the membrane and preventing the calcium ion influx necessary for the initiation of contraction.

Routes of administration/doses

Sodium nitroprusside should be administered through a dedicated vein using a controlled infusion device at the rate of 0.5–6 micrograms/kg/min, titrated according to response. Invasive arterial pressure measurement during the use of the drug is considered mandatory. Onset of action is almost immediate; the desired response is usually achieved in 1–2 minutes.

Effects

CVS



In hypertensive and normotensive patients, infusion of the drug causes a decrease in the systemic blood pressure and a compensatory tachycardia; the cardiac output is usually well maintained. In patients with heart failure, cardiac output increases due to a decrease in both venous return and systemic vascular resistance. The myocardial wall tension is decreased and myocardial oxygen consumption falls; the heart rate tends to decrease due to improved haemodynamics with the use of the drug. The blood pressure is usually well maintained under these circumstances. Myocardial contractility is unaltered by the drug.

RS

Sodium nitroprusside causes a reversible decrease in PaO_2 due to attenuation of hypoxic pulmonary vasoconstriction; an increased inspired oxygen concentration may be necessary.

CNS

The drug causes cerebral vasodilation, leading to an increase in intracranial pressure in normocapnic patients; a 'steal' phenomenon may occur. The autoregulatory curve is shifted to the left.

AS

Sodium nitroprusside decreases to lower oesophageal sphincter pressure and may cause a paralytic ileus.

GU

The renal blood flow and glomerular filtration rate are well maintained during infusions of the drug.

Metabolic/other

A compensatory increase in plasma catecholamine concentration and plasma renin activity occurs during the use of the drug. A metabolic acidosis may also occur.

Toxicity/side effects

The major disadvantage of the drug is its liability to produce cyanide toxicity, the likelihood of which is increased by hypothermia, malnutrition, vitamin B12 deficiency, and severe renal or hepatic impairment. Cyanide ion toxicity is related to the rate of infusion of sodium nitroprusside rather than to the total dose used; however, it is recommended that no more than 1.5 mg/kg of the drug is infused acutely and no more than 4 micrograms/kg/min is used chronically. The cyanide ion combines with cytochrome C and leads to impairment of aerobic metabolism; metabolic acidosis due to an increased serum lactic acid concentration may result. The signs of cyanide ion toxicity are tachycardia, dysrhythmias, hyperventilation, sweating, and the development of a metabolic acidosis; these occur at plasma cyanide ion concentrations in excess of 8 micrograms/ml. Treatment of cyanide ion toxicity involves curtailing the infusion of sodium nitroprusside, general supportive measures, and the administration of sodium thiosulphate or dicobalt edetate.

Additionally, profound hypotension produced by the drug may manifest itself as nausea and vomiting, abdominal pain, restlessness, headache, dizziness, palpitations, and retrosternal pain.

Kinetics

Pharmacokinetic data are difficult to obtain due to the very short duration of action of the drug.

Absorption

The drug is not absorbed orally.

Distribution

Sodium nitroprusside in the blood is confined essentially to the plasma; scarcely any is present within red blood cells. The V_D is approximately the same as the extracellular space (15 l).

Metabolism

Occurs by two separate pathways: in the presence of low plasma concentrations of sodium nitroprusside, the predominant route appears to be by reaction with the sulphydryl groups of amino acids present in the plasma. In the presence of higher plasma concentrations of the drug, rapid non-enzymatic hydrolysis occurs within red blood cells. Five cyanide ions are produced by the degradation of each molecule of sodium nitroprusside; one reacts with methaemoglobin to form cyanomethaemoglobin. The remaining four cyanide ions enter the plasma; 80% of these react with thiosulphate in a reaction catalyzed by hepatic rhodanese to form thiocyanate. The remainder of the cyanide ions reacts with hydroxycobalamin to form cyanocobalamin (vitamin B12).

Excretion

Both thiocyanate and cyanocobalamin are excreted unchanged in the urine. The elimination half-life of the former is 2.7 days.

Special points

Sodium nitroprusside is removed by haemodialysis.

Sodium valproate

Uses

Sodium valproate is used in the treatment of:

1. primary generalized epilepsies, especially petit mal epilepsy, myoclonic seizures, infantile spasms, and tonic-clonic epilepsy
2. chronic pain of non-malignant origin.

Chemical

Sodium valproate is the sodium salt of valproic acid, a fatty (carboxylic) acid.

Presentation

As 100/200/500 mg tablets, a syrup containing 40 mg/ml, and in ampoules containing 400 mg of lyophilized sodium valproate for dilution in 4 ml of water.

Main action

Anticonvulsant.

Mode of action

The most likely mode of action is via GABA-ergic inhibition; sodium valproate increases brain GABA levels by inhibition of succinic semialdehyde dehydrogenase in the GABA shunt. Alternatively it may:

1. mimic the action of GABA at post-synaptic receptors and
2. reduce excitatory inhibition (especially that due to aspartate).

Routes of administration/doses

The adult oral dose is 600–2500 mg daily in two divided doses. The intravenous dose is 400–2500 mg daily in divided doses. The effective plasma range is 40–100 mg/l.

Effects

CNS

The drug has anticonvulsant properties as described. Sodium valproate produces minimal sedation; an essential tremor may occasionally develop with the use of the drug.

Metabolic/other

Hyperammonaemia occurs infrequently.

Toxicity/side effects

Sodium valproate is generally well tolerated. Hepatic dysfunction, acute pancreatitis, gastrointestinal upsets, hair loss, oedema, and weight gain may occur following administration of the drug. There are also reports of platelet disturbances (decreased platelet aggregation and thrombocytopaenia) and coagulation disturbances (increased bleeding time, prothrombin time, and partial activated thromboplastin time) complicating the administration of sodium valproate.

Kinetics

Absorption

Sodium valproate is rapidly and completely absorbed; the oral bioavailability is virtually 100%.

Distribution

The drug is 90% protein-bound in the plasma, predominantly to albumin; the V_D is 0.1–0.41 l/kg. Brain concentrations are 7–28% of plasma levels.

Metabolism

Sodium valproate is almost completely metabolized in the liver by oxidation and glucuronidation; some of the metabolites are active.

Excretion

1–3% is excreted unchanged in the urine. The clearance is 7–11 ml/kg/hour and the elimination half-life is 8–20 hours.

Special points

High concentrations of sodium valproate displacethiopental from its binding sites *in vitro* and similarly displace diazepam

in vivo. Platelet function may need to be monitored prior to surgery or epidural or spinal anaesthesia. The drug is contraindicated in patients with acute liver disease and liver function should be monitored during chronic therapy. The sedative effects of the drug are additive with those of other central nervous system depressants.

Sodium valproate is not removed by dialysis.

Spironolactone

Uses

Spironolactone is used in the treatment of:

1. congestive cardiac failure
2. hepatic cirrhosis with ascites and oedema
3. refractory oedema
4. hypertension
5. the nephrotic syndrome
6. in combination with loop or thiazide diuretics to conserve potassium and
7. in the diagnosis and treatment of Conn's syndrome.

Chemical

A synthetic steroid.

Presentation

As 25/50/100 mg tablets of spironolactone. Fixed dose combinations with hydroflumethiazide or furosemide are also available.

Main actions

Diuretic.

Mode of action

Spironolactone acts as a competitive antagonist of aldosterone at the latter's receptor site in the distal convoluted tubule; consequently, sodium ion reabsorption is inhibited and potassium ion reabsorption is increased. The drug thus promotes saliuresis and also potentiates that produced by other diuretic agents.

Routes of administration/doses

The adult oral dose of spironolactone is 100–400 mg daily; the corresponding dose of potassium canrenoate is 200–800 mg administered by slow intravenous infusion. The drug has a slow onset of action; the diuretic effect takes 3 to 4 days to become established.

Effects

CVS

The drug has an antihypertensive effect that may be mediated by alteration of the extracellular:intracellular sodium ion gradient or by antagonism of the effect of aldosterone on arteriolar smooth muscle.

CNS

Spironolactone may produce both sedation and muscular weakness, presumably secondarily to electrolyte derangements.

GU

The principal effect of the drug is diuresis with retention of potassium ions. The renal blood flow and glomerular filtration rate are unaffected although the free water clearance may increase.

Metabolic/other

Spironolactone has an anti-androgenic effect due to inhibition of ovarian androgen secretion and interference with the peripheral action of endogenous androgens. The drug increases renal calcium ion excretion and may also lead to a reversible hyperchloraemic metabolic acidosis and an increased plasma urea concentration.

Toxicity/side effects

The predominant side effect of spironolactone is hyperkalaemia, especially in the presence of renal impairment. The use of the drug is also associated with an appreciable incidence of nausea and vomiting and other gastrointestinal disturbances. Menstrual irregularities in the female and gynaecomastia in the male may result from the anti-androgenic effects of spironolactone.

Kinetics

Absorption

Spironolactone is incompletely absorbed when administered orally and has a bioavailability by this route of 70%; the drug undergoes extensive first-pass hepatic metabolism.

Distribution

The drug is 90% protein-bound in the plasma.

Metabolism

Spironolactone is rapidly and extensively metabolized by deacetylation and dethiolation; some of the metabolites, including canrenone, are active.

Excretion

The metabolites are principally excreted in the urine, with a small proportion undergoing biliary excretion. The elimination half-life of spironolactone is 1–2 hours.

Special points

Spironolactone decreases the responsiveness to co-administered pressor agents and increases the effects of co-administered cardiovascular depressants, including anaesthetic agents. The drug increases the serum concentrations of co-administered digoxin and may interfere with digoxin assay techniques.

SSRIs

Uses

Selective serotonin re-uptake inhibitors (SSRIs) are used in the treatment of:

1. unipolar depression
2. obsessive-compulsive disorder
3. generalized anxiety disorder
4. social anxiety disorder
5. panic disorder
6. post-traumatic stress disorder and
7. bulimia nervosa.

Chemical

SSRIs have a variety of chemical structures.

Presentation

The following SSRIs are in common clinical use and are available in tablet or capsule form: fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram, and escitalopram.

Main action

Antidepressant and anxiolytic.

Mode of action

SSRIs selectively inhibit the neuronal re-uptake of serotonin by the pre-synaptic serotonin re-uptake pump. *In vitro*, they exhibit very weak anticholinergic and histaminergic activity.

Route of administration/doses

SSRIs are usually administered orally as a single daily dose in the mornings. The specific dose of an SSRI administered is dependent on the clinical indication, age of the patient, and particular agent being used.

Effects

CVS

SSRIs may cause an increase or decrease in heart rate together with a fall in blood pressure which may be postural in nature.

CNS

The effects of SSRIs are to improve mood and decrease feelings of anxiety.

Metabolic/other

SSRIs may cause a decrease in plasma sodium concentration, possibly causing inappropriate ADH secretion. These drugs should be used with caution in patients concurrently receiving diuretics.

Toxicity/side effects

SSRIs cause dose-related gastrointestinal effects (nausea, abdominal pain, diarrhoea). Hypersensitivity reactions of all types may occur. Urogenital side effects have been reported, including reduced libido, anorgasmia, impotence, and urinary frequency or retention.

Kinetics

Absorption

SSRIs are well absorbed from the gastrointestinal tract. They undergo extensive first-pass metabolism, except for citalopram.

Distribution

Due to the lipophilic nature of SSRIs, these drugs have large volumes of distribution and consequently, take some time to reach a steady-state concentration.

Metabolism

SSRIs undergo extensive hepatic metabolism via the cytochrome P450 system. In addition, the drugs are potent inhibitors of certain CYP isoenzymes, including CYP2D6. Fluoxetine is metabolized to the active metabolite, norfluoxetine.

Excretion

Metabolites undergo renal elimination.

Special points

All SSRIs are associated with a withdrawal syndrome if treatment is discontinued abruptly. The commonest symptoms include: nausea, vomiting, headache, paraesthesia, dizziness, sweating, sleep disturbances, and anxiety.

Concurrent administration of SSRIs to patients receiving MAOIs, lithium, L-tryptophan, sumatriptan, risperidone, or MDMA may lead to serotonin syndrome. Serotonin syndrome is characterized by the acute onset of the following symptoms and signs: tachycardia, hypertension, hyperthermia, sweating, nausea, diarrhoea, agitation, pupillary dilatation, myoclonus, and hyperreflexia.

Starches

Uses

Starches are used as plasma volume substitutes to expand and maintain circulating blood volume.

Chemical

Hydroxyethyl starches (HES) are derived from amylopectin. The hydroxyethyl groups are substituted into the glucose units to retard degradation by serum amylase. Differentiation of HES products is based on molecular weight and degree of substitution of hydroxyethyl groups to glucose subunits. A HES molecule with 7 substitutions per 10 glucose subunits has the prefix heta-, with 6 substitutions has the prefix hexa-, with 5 substitutions has the prefix penta-, and with 4 substitutions has the prefix tetra-. Details of a HES product are presented with a description of the molecular weight followed by the degree of substitution (i.e. molecular weight (kDa)/degree of substitution)

Presentation

A number of agents are available in the UK for intravenousadministration. Examples of commercially available products include:

- Hespan® 6%—hetastarch (450/0.7)
- EloHAES® 6%—hexastarch (200/0.6)
- Hemohes® 6%/10%, HAES-steril® 6%/10%—pentastarches (200/0.5)
- Venofundin® 6%, Voluven® 6%—tetrastarches (130/0.4).

The above agents are presented in 0.9% sodium chloride for intravenous infusion. The following agents contain HES in the corresponding solvents:

- Tetraspan® 6%/10% (130/0.42): Na^+ 140 mmol/l, K^+ 4.0 mmol/l, Ca^{2+} 2.5 mmol/l, Mg^{2+} 1.0 mmol/l, Cl^- 118 mmol/l, acetate 24 mmol/l, osmolarity 297 mOsm/l, pH 5.6–6.4
- Volulyte® 6% (130/0.4): Na^+ 137 mmol/l, K^+ 4.0 mmol/l, Mg^{2+} 1.5 mmol/l, Cl^- 110 mmol/l, CH_3COO^- 34 mmol/l, osmolarity 286.5 mOsm/l, pH 5.7–6.5
- HyperHAES® 6% (200/0.5): hypertonic 7.2% sodium chloride (Na^+ 1232 mmol/l, Cl^- 1232 mmol/l, osmolarity 2464 mOsm/l, pH 3.5–6).

Main action

Intravascular volume expansion.

Mode of action

Temporary increase in plasma oncotic pressure.

Route of administration/dose

The specific dose of an agent administered is dependent on the clinical indication, the haemodynamic status of the patient, and particular agent being used. Maximum daily doses are as follows: HES (130/0.5), 50 ml/kg/day; HES (200/0.5) 6%, 33 ml/kg/day; HES (200/0.5) 10%, 20 ml/kg/day; HyperHAES® 6% (200/0.5), 4 ml/kg bolus dose only.

Effects

CVS

The haemodynamic effects of starches are proportional to the prevailing circulating volume. The duration of action of these agents depends on the specific agent in use. HES derivatives with a high molecular weight and degree of substitution are present in the plasma for longer with a corresponding effect on haemodynamics.

Toxicity/side effects

The most important side effect is that of overtransfusion, leading to pulmonary oedema. Administration of HES dissolved in saline-containing solvents may lead to a hypernatraemic hyperchloraemic metabolic acidosis. Starches may affect coagulation mechanisms, depending on the agent being used. Substances with a high molecular weight and degree of substitution have a greater effect on coagulation, including decreased levels of fibrinogen, factor VIII, vWF, and decreased platelet function. HES derivatives have been associated with renal impairment although the mechanism of HES-related nephropathy remains to be fully elucidated. Pruritus may result from the administration of HES. Allergic reactions have been reported following the use of these agents.

Kinetics

Data are incomplete.

Distribution

Following administration of HES 130/0.4, 75% of the dose administered is present within the plasma at 30 minutes, with 14% present at 6 hours. HES 130/0.4 exhibits non-linear pharmacokinetics with a half-life (alpha) of 1.4 hours and a half-life (beta) of 12.1 hours.

Following administration of HES 200/0.5 (6%), 68% of the dose administered is present within the plasma at 1 hour, with 27% present at 6 hours and 16% at 12 hours.

Following rapid administration of HES 200/0.5 (10%), the plasma volume increases to a final 145% over 1 hour, followed by a decrease in plasma volume to 75% at 6 hours. 78% of an administered dose is present within the plasma at 1 hour, with 34% present at 6 hours and 18% at 12 hours.

Administration of HyperHAES® results in a rapid expansion of the intravascular plasma volume that is short-lived.

Large HES molecules enter the reticuloendothelial system and undergo metabolism in the liver and spleen.

Metabolism

Starches are metabolized via alpha- (plasma) and gamma- (intracellular) amylases into oligosaccharides and polysaccharides of various molecular weights.

Excretion

HES metabolites are renally excreted.

Statins

Uses

Statins are used in the treatment of:

1. hypercholesterolaemia
2. primary prevention of cardiovascular events
3. secondary prevention of cardiovascular events.

Chemical



Naturally occurring or synthetically derived inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCoA).

Presentation

Six agents are available in the UK for oral administration. Atorvastatin and simvastatin comprise approximately 85% of statins prescribed in the UK.

Main action

Reduction in total cholesterol.

Mode of action

Inhibition of HMGCoA reductase, leading to early blockade of conversion of HMGCoA to mevalonate, thereby preventing subsequent conversion to cholesterol and isoprenoids.

Route of administration/doses

The specific dose of an agent administered is dependent on the clinical indication and particular agent being used. Statins are administered orally, usually at night.

Toxicity/side effects

The most important side effect of statin therapy is muscle pains which may be associated with a myopathy with subsequent development of rhabdomyolysis and acute renal failure secondary to myoglobinuria. Sleep disturbance, memory loss, sexual dysfunction, depression, and rarely, interstitial lung disease have all been reported following use of these drugs. Hepatic serum transaminases may become elevated during treatment.

Kinetics

Absorption

The bioavailability of statins is variable, depending on the specific agent. Atorvastatin has a bioavailability of 12%, simvastatin a bioavailability of 5%. Statins undergo extensive first-pass metabolism.

Distribution

Statins are highly protein-bound in the plasma (90–98%), apart from pravastatin which has protein binding of 43–67%.

Metabolism

The majority of statins are metabolized via the cytochrome P450 enzyme system. Atorvastatin and simvastatin are metabolized by CYP3A4. Atorvastatin is metabolized to orthohydroxylated and parahydroxylated metabolites during first-pass metabolism, which are pharmacologically active. Simvastatin is an inactive lactone that is metabolized during first-pass metabolism to the active metabolite, beta-hydroxyacid.

Excretion

The half-life of atorvastatin is 15 hours and that of simvastatin 1.9 hours. Up to 20% of a dose may be excreted renally. The majority of metabolites undergo biliary excretion. Minimal enterohepatic circulation occurs.

Special points

There is growing evidence to suggest that statins act as inhibitors of the inflammatory process. Statins reduce leukocyte adhesion to endothelial cells during sepsis-driven leukocyte activation. The drugs also downregulate the production of the following pro-inflammatory cytokines: IL-6, IL-8, TNF-alpha, monocyte chemoattractant protein-1, and CRP. Statins also appear to reduce the procoagulant effects seen in sepsis and have anti-inflammatory effects mediated through upregulation of endothelial NO synthase activity, thereby enhancing NO production.

Co-administration of agents that act as CYP3A4 inhibitors may lead to increased drug levels of statins and a corresponding increased risk in the development of myopathy/rhabdomyolysis. The following agents require either discontinuation of statin therapy or dose reduction, depending on the specific drug(s) being used: itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, ciclosporin, diazole, amiodarone, verapamil, diltiazem, grapefruit juice.

Sucralfate

Uses

Sucralfate is used:

1. in the treatment of peptic ulcer disease and
2. for the prevention of stress ulceration in the critically ill.

Chemical

An aluminium salt of sulphated sucrose.

Presentation

As tablets containing 1 g sucralfate and a white, viscous suspension containing 200 mg/ml of sucralfate.

Main actions

Cytoprotection of the upper gastrointestinal tract.

Mode of action

At acid pH, sucralfate forms a viscous paste which adheres preferentially to peptic ulcers via ionic binding. It acts by providing a physical barrier to the diffusion of acid, pepsin, and bile salts and also by forming complexes with proteins at the ulcer surface, which resist peptic hydrolysis.

Routes of administration/doses

The adult dose for the prophylaxis of stress ulceration is 1 g 6-hourly.

Effects

AS

Sucralfate has weak intrinsic antacid activity. It has no effect on gastric emptying time. The drug increases gastric blood flow and enhances gastric epithelial proliferation via stimulation of gastric mucosal epidermal growth factor and fibroblast growth factor.

Metabolic/other

In uraemic patients, sucralfate increases aluminium absorption and therefore, should be used with care. It acts as a phosphate binder which may induce hypophosphataemia.

Toxicity/side effects

Sucralfate is essentially non-toxic. Constipation occurs in 2%.

Kinetics

Absorption

Sucralfate is minimally (3–5%) absorbed after oral administration.

Distribution

85–95% of an oral dose remains in the gastrointestinal tract. The V_D and percentage of protein binding are unknown.

Metabolism

No metabolism of the drug occurs in man.

Excretion

Predominantly unchanged in the faeces. The fraction that is absorbed is excreted primarily in the urine.

Sufentanil

Uses

Sufentanil is used for:

1. the induction and maintenance of general anaesthesia and has been used for
2. post-operative analgesia.

Chemical

A phenylpiperidine which is the thienyl derivative of fentanyl.



Presentation

As a clear solution containing 50 micrograms/ml of sufentanil citrate. The drug is not commercially available in the UK.

Main actions

Analgesia and respiratory depression.

Mode of action

Sufentanil is a highly selective mu-agonist; the mu-opioid receptor appears to be specifically involved in the mediation of analgesia. Part of the analgesic effect of the drug may be attributable to stimulation of 5HT release. Opioids appear to exert their effects by increasing intracellular calcium concentration which, in turn, increases potassium conductance and hyperpolarization of excitable cell membranes. The decrease in membrane excitability that results may decrease both pre- and post-synaptic responses.

Routes of administration/doses

The intravenous dose is 0.5–50 micrograms/kg and the adult dose via the epidural route is 10–100 micrograms (the optimal post-operative dose being 30–50 micrograms). When administered intravenously, the drug acts in 1–6 minutes and the duration of effect is 0.5–8 hours, dependent on the other components of the anaesthetic.

Effects

CVS

Sufentanil causes little haemodynamic disturbance. Heart rate and blood pressure tend to decrease immediately post-induction. Venous pooling may lead to orthostatic hypotension.

RS

The drug produces dose-dependent respiratory depression which may be delayed in onset. Chest wall rigidity (the ‘wooden chest’ phenomenon) may occur after the administration of sufentanil—this may be an effect of the drug on mu-receptors located on GABA-ergic interneurons.

CNS

Sufentanil is 2000–4000 times as potent an analgesic as morphine. The EEG changes produced by the drug are similar to those produced by fentanyl: initial beta activity is decreased and alpha activity is increased; subsequently, alpha activity disappears and delta activity predominates. The drug has no intrinsic effect on intracranial pressure. Miosis is produced as a result of stimulation of the Edinger–Westphal nucleus.

AS

Sufentanil appears to cause less nausea than fentanyl. The drug may cause spasm of the sphincter of Oddi.

Metabolic/other

The drug tends to obtund the stress response to surgery although it does not completely abolish it. Sufentanil may cause histamine release and may have less effect on immune function than fentanyl.

Toxicity/side effects

Hypotension, tachycardia, bradycardia, nausea, and the 'wooden chest' phenomenon are the side effects most commonly reported with the use of sufentanil. Tonic/clonic movements of the limbs have also been reported.

Kinetics

Absorption

The drug is normally administered intravenously; the drug is, however, 20% absorbed when administered transdermally.

Distribution

Sufentanil is 92% protein-bound in the plasma, predominantly to alpha-1 acid glycoprotein. The drug is highly lipophilic; the V_D is 1.74–5.17 l/kg.

Metabolism

The metabolic pathways are unknown in man although two metabolites (norsufentanil and desmethylsufentanil) have been identified in the urine.

Excretion

60% of an administered dose appear in the urine and 10% in bile. The clearance is 11–21 ml/min/kg; the elimination half-life is 119–175 minutes.

Special points

Sufentanil decreases the MAC of co-administered volatile agents by 60–70%. The drug should be used with caution in the presence of renal or hepatic failure although the kinetics appears to be unaltered.

The drug increases the effect of non-depolarizing muscle relaxants to a similar extent to halothane.

Sugammadex

Uses

Sugammadex is used to reverse neuromuscular blockade induced by rocuronium or vecuronium.

Chemical

A modified gamma-cyclodextrin.

Presentation

As a clear colourless or pale yellow solution for injection, available in 2 ml and 5 ml glass vials, containing 100 mg/ml of sugammadex sodium (equivalent to sugammadex 100 mg/ml) needing to be stored below 30°C. It has a pH of between 7 and 8 and an osmolality of between 300 and 500 mOsm/kg. One ml of solution contains 9.7 mg of sodium. The solution may also contain 3.7% hydrochloric acid and/or sodium hydroxide for pH adjustment.

Main action

Reversal of neuromuscular blockade induced by rocuronium or vecuronium.

Mode of action

Sugammadex acts by encapsulating the steroid portion of aminosteroidal molecules within its hydrophobic interior. The negatively charged carboxyl groups bind to the positively charged nitrogen atom on the aminosteroidal molecule. This binding of the neuromuscular blocking (NMB) drug decreases the amount of free drug within the central compartment, thereby establishing a concentration gradient and resulting in the movement of NMB drug away from the effector site towards the central compartment. The resultant reduction in competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction leads to successful binding of acetylcholine and rapid re-establishment of neuromuscular function.

Route of administration/doses

The drug is administered intravenously as a single bolus injection in a variety of doses depending on the extent of neuromuscular blockade present in a given patient. A dose of 4 mg/kg is recommended when recovery of neuromuscular function has reached at least 1–2 post-tetanic counts following administration of rocuronium or vecuronium (i.e. 'deep' neuromuscular block). The median time to recovery of the T4/T1 ratio to 0.9 is 3 minutes. A lower dose of 2 mg/kg is recommended when recovery of neuromuscular function has reached at least the reappearance of T2 (i.e. 'shallow' neuromuscular block) with a median time to recovery of T4/T1 ratio to 0.9 is 2 minutes. The median recovery time is slightly faster in patients who have received rocuronium compared to those receiving vecuronium. Sugammadex may also be administered immediately following the administration of rocuronium as part of a modified rapid sequence induction (i.e. 'rescue reversal') when a 'can't intubate, can't ventilate' scenario has occurred. The

recommended dose for 'rescue reversal' is 16 mg/kg. Following the administration of 1.2 mg/kg of rocuronium, if sugammadex is given 3 minutes later, the median time to recovery of the T4/T1 ratio to 0.9 is approximately 1.5 minutes. Sugammadex is not recommended for use in 'rescue reversal' following the administration of vecuronium. In the event of the re-establishment of neuromuscular block, a second dose of 4 mg/kg of sugammadex is recommended. The recommended dose for reversal in children aged between 2 and 17 years, when the recovery of neuromuscular function has reached at least the reappearance of T2, is 2 mg/kg. Use of the drug is not currently recommended in other reversal situations including 'rescue reversal'. Sugammadex is not currently recommended for use in newborns and infants.

Effects

CVS

Sugammadex has minimal cardiovascular side effects. There is no significant prolongation of the QT interval.

RS

The drug has no respiratory effects.

CNS

The drug has no effect on intracranial or intraocular pressure.

AS

Administration of the drug may lead to a bitter or metallic taste.

Toxicity/side effects

There has been one report of a patient developing symptoms of flushing, tachycardia, and palpitations following the administration of 8.4 mg/kg of sugammadex. These symptoms were confirmed to be that of an allergic reaction and were self-limiting.

Kinetics

Distribution

Sugammadex and the sugammadex-NMB complex do not bind to plasma proteins or erythrocytes. The V_D is 11–14 l and the drug exhibits linear kinetics in the dosage range of 1–16 mg/kg.

Metabolism

The drug does not undergo metabolism within the human body.

Excretion

The clearance is 88–120 ml/min and the elimination half-life is 1.8 hours. More than 90% of a given dose is excreted within 24 hours. 96% of the dose is excreted in the urine with up to 95% as unaltered drug. Excretion via faeces or expired air was less than 0.02% of the dose in clinical studies.

Special points

In patients with mild and moderate renal impairment, no alteration in dosage is required. In patients with severe renal impairment, the excretion of sugammadex and the sugammadex-NMB complex is prolonged and use of the drug is not recommended. The clearance of sugammadex by haemodialysis is variable.

No dose reduction is recommended in elderly patients, although the time to recovery of the T4/T1 ratio to 0.9 may be slightly prolonged.

No dose alteration is required for patients with mild and moderate hepatic impairment. No data is currently available in patients with severe hepatic impairment and the use of sugammadex is not recommended.

Dose calculation in obese patients should be made based on actual body weight.

Reoccurrence of neuromuscular block following the administration of sugammadex has been reported as usually being due to sub-optimal dosing of the drug. However, administration of drugs in the immediate post-operative period that potentiate the effects of neuromuscular block may theoretically lead to reoccurrence of block and should be used in caution in patients who have received sugammadex. In addition, displacement of bound NMB from sugammadex may theoretically occur, leading to reoccurrence of neuromuscular blockade if the following drugs are administered with 6 hours of a patient receiving sugammadex: toremifene, flucloxacillin, fusidic acid.

If neuromuscular blockade is required following reversal with sugammadex, then a non-steroidal agent (e.g. suxamethonium or a benzoisoquinolinium agent) should be used due to the risk of reduced efficacy of standard doses of rocuronium or vecuronium in the presence of residual sugammadex. A delay of 24 hours is recommended prior to repeat administration of rocuronium or vecuronium following the use of sugammadex.

Due to the steroid binding ability of sugammadex, the drug may interact with hormonal contraceptive agents. Administration of the drug may lead to a decrease in progesterone exposure (34% decrease) equivalent to missing one daily dose. It is recommended that patients taking oral hormonal contraceptive agents should consult the 'missed daily dose' advice contained in the product information leaflet. Patients receiving non-oral hormonal contraceptive agents should be advised to use an additional non-hormonal contraceptive method for the following 7 days after administration of sugammadex.

There is some evidence that sugammadex may interfere with the following laboratory tests: serum progesterone, activated partial thromboplastin time, prothrombin time. Data suggests that interference with these tests occurs following a dose of 16 mg/kg of sugammadex. The clinical relevance of this is uncertain.

Sulphonylureas

Uses

Sulphonylureas are used in the treatment of non-insulin-dependent (type II) diabetes mellitus.

Chemical

An S-phenylsulphonylurea structure with substitutions on the phenyl ring and urea terminus.

Presentation

Three generations of sulphonylureas exist:

1. first-generation: tolbutamide
2. second-generation: gliclazide, glibenclamide
3. third-generation: glimepiride.
4. All are presented in tablet form. There is a modified release preparation of gliclazide.

Main action

Hypoglycaemia.

Mode of action

Sulphonylureas act by liberating insulin from pancreatic beta-cells; they appear to act by binding to the plasma membrane of the beta-cell and producing prolonged depolarization, reducing the permeability of the membrane to potassium. This in turn leads to opening of calcium channels; the resulting influx of calcium causes triggering of insulin release.

Route of administration/doses

These agents are only available for oral administration. The specific dose and frequency of an agent administered is dependent on the clinical indication and particular agent being used.

Effects

Metabolic/other

Sulphonylureas cause a decrease in plasma triglyceride, cholesterol, and free fatty acid concentrations. Gliclazide decreases the incidence of microthrombosis by two methods, firstly by partial inhibition of platelet aggregation and adhesion and secondly by an action on vascular endothelium fibrinolytic activity with an increase in tissue plasminogen activator activity. Glimepiride has extrapancreatic effects. It increases the number of active glucose transport molecules in addition to increasing the activity of the glycosyl phosphatidylinositol-specific lipase C, which may be correlated with drug-induced lipogenesis and glycogenesis in fat and muscle cells. The drug also inhibits hepatic gluconeogenesis by increasing the intracellular concentration of fructose-2,6-bisphosphate.

Toxicity/side effects

Hypoglycaemia is a common complication of sulphonylurea therapy. Gastrointestinal disturbances, cholestatic jaundice, and alterations in liver function tests may complicate the use of sulphonylureas. Leucopaenia and thrombocytopaenia have also been reported. Sulphonylureas are potentially teratogenic.

Kinetics

Absorption

Sulphonylureas are well absorbed from the gastrointestinal tract. Gliclazide and glimepiride have a 100% bioavailability.

Distribution

The V_D of these agents is variable: gliclazide V_D 0.42 l/kg, glibenclamide V_D 0.15 l/kg, glimepiride V_D 0.12 l/kg. Protein-binding is high with 95–99% of agents bound to albumin.

Metabolism

Sulphonylureas undergo extensive hepatic metabolism via CYP2C9 to inactive metabolites.

Excretion

30–50% of an administered dose is excreted in the urine, the remainder in the faeces. Clearance and elimination half-lives of the individual drugs vary: the half-life of gliclazide is 12–20 hours, that of glibenclamide is 1–2 hours and of glimepiride is 5–8 hours. The elimination of these agents is impaired in the presence of severe renal impairment.

Special points

The following drugs may potentiate the effect of sulphonylureas either by displacement from plasma proteins or by inhibition of their hepatic metabolism, resulting in hypoglycaemia: NSAIDs, salicylates, sulphonamides, oral anticoagulants, monoamine oxidase inhibitors, and beta-adrenergic antagonists. Conversely, the following drugs tend to counteract the effect of sulphonylureas and result in loss of diabetic control: thiazide and other diuretics, steroids, phenothiazines, phenytoin, sympathomimetic agents, and calcium antagonists.

The long-acting sulphonylureas should be stopped prior to anaesthesia for major surgery due to the risk of hypoglycaemia. Alternative methods of blood sugar control may need to be instituted.

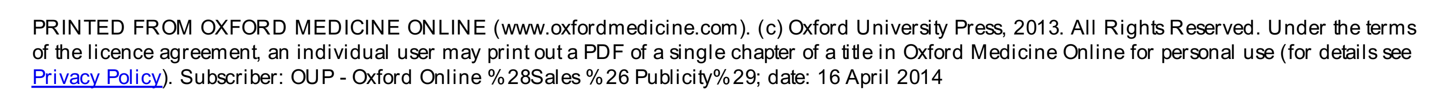
Suxamethonium

Uses

Suxamethonium is used:

1. wherever rapid and profound neuromuscular blockade is required, e.g. to facilitate tracheal intubation and
2. for the modification of fits after electroconvulsive therapy.

Chemical



The dicholine ester of succinic acid (equivalent to 2 acetylcholine molecules joined back-to-back).

Presentation

As a clear aqueous solution containing 50 mg/ml of suxamethonium chloride; the preparation should be stored at 4°C.

Main actions

Neuromuscular blockade of brief duration in skeletal muscle.

Mode of action

Suxamethonium causes prolonged depolarization of skeletal muscle fibres to a membrane potential above which an action potential can be triggered.

Routes of administration/doses

The intravenous dose is 0.5–2.0 mg/kg; the onset of action occurs within 30 seconds and the duration of action is 3–5 minutes. Infusion of a 0.1% solution at 2–15 mg/kg/hour will yield 90% twitch depression. The intramuscular dose is up to 2.5 mg/kg. Equal doses on a mg/kg basis have a shorter duration of action in infants. The drug may also be administered sublingually at a dose of 2 mg/kg.

Effects

CVS

With repeated doses of suxamethonium, bradycardia and a slight increase in mean arterial pressure may occur.

RS

Apnoea occurs subsequent to skeletal muscle paralysis.

CNS

The administration of suxamethonium may initially cause fasciculations which are then followed by a phase I depolarizing block. The characteristics of this during partial paralysis are:

1. a well-sustained tetanus during stimulation at 50–100 Hz
2. the absence of post-tetanic facilitation
3. a train-of-four ratio >0.7 and
4. potentiation by anticholinesterases.

With repeated administration or a large total dose, a phase II block may develop. The characteristics of this during partial paralysis are:

1. a poorly sustained tetanus
2. post-tetanic facilitation
3. a train-of-four ratio <0.3
4. reversal by anticholinesterases and
5. tachyphylaxis.

Intracranial and intraocular pressures are both raised following the administration of suxamethonium.

AS

The intragastric pressure increases by 7–12 cmH_2O; the lower oesophageal sphincter tone simultaneously decreases with the use of suxamethonium. Salivation and gastric secretions are increased.

Metabolic/other

Serum potassium concentration is briefly increased in normal individuals by 0.2–0.4 mmol/l.

Toxicity/side effects

Bradycardia and other dysrhythmias may occur with single or repeated dosing. The hyperkalaemic response is markedly exaggerated in patients with burns or major denervation of muscle and acute or chronic renal failure; this may lead to cardiac arrest. Post-operative muscular pains are common, especially in women, the middle-aged, and those ambulant early in the post-operative period. Intraocular pressure is transiently raised following the use of suxamethonium—the drug should be used with caution in patients with penetrating eye injuries. Suxamethonium is a potent trigger agent for the development of malignant hyperthermia and may cause generalized contractures in those patients exhibiting myotonia. Prolonged apnoea may occur in susceptible individuals. There have been many reports of fatal anaphylactoid reactions with the administration of suxamethonium. Cross-sensitivity exists with many of the non-depolarizing drugs following administration of suxamethonium.

Kinetics

Distribution

An initial rapid redistribution phase may contribute to the brief duration of action of the drug. Suxamethonium appears to be protein-bound to an unknown extent.

Metabolism

The drug is hydrolyzed by plasma cholinesterase (EC 3.1.1.8) to succinylomonocholine (which is weakly active) and choline; the former is further hydrolyzed by plasma cholinesterase to succinic acid and choline. 80% of an administered dose is hydrolyzed before it reaches the neuromuscular junction.

Excretion

2–10% of an administered dose is excreted unchanged in the urine. The *in vivo* hydrolysis rate is 3–7 mg/l/min and the half-life 2.7–4.6 minutes.

Special points

The incidence of muscle pains after the administration of suxamethonium may be decreased by pre-treatment with:

1. a low (0.2 mg/kg) dose of suxamethonium
2. a small dose of a non-depolarizing relaxant
3. diazepam
4. dantrolene
5. aspirin or
6. vitamin C.

Plasma cholinesterase activity may be influenced by both genetic and acquired factors, leading to an altered pattern of response to suxamethonium. The normal gene encoding for plasma cholinesterase is E_l^u (usual); three abnormal genes also exist: E_l^a (atypical), E_l^s (silent), and E_l^f (fluoride-resistant).

Simple Mendelian genetics are involved; 94% of the population is heterozygous for the usual gene and are clinically normal in their response to suxamethonium. E_l^a homozygotes comprise 0.03%, E_l^s homozygotes 0.001%, and E_l^f homozygotes 0.0003% of the population, and all remain apnoeic for 1–2 hours after receiving the drug and develop a phase II block during this period (fresh frozen plasma may be used to provide a source of plasma cholinesterase under these circumstances). All possible combinations of heterozygotes exist—they constitute 3.8% of the population and remain apnoeic for approximately 10 minutes after receiving suxamethonium.

In addition, plasma cholinesterase concentrations may be reduced in pregnancy, liver disease, cardiac or renal failure, hypoproteinaemic states, carcinomatosis, thyrotoxicosis, tetanus, muscular dystrophy, and in patients with burns, and suxamethonium may have a prolonged action in these states. Drugs which decrease the activity of plasma cholinesterase include ecothiopate, tacrine, procaine, lidocaine, lithium and magnesium salts, ketamine, pancuronium, the oral contraceptive pill, and cytotoxic agents. Suxamethonium does not appear to be potentiated by volatile agents although phase II block may appear more readily in their presence.

Suxamethonium is pharmaceutically incompatible with thiopental. The effects of digoxin may be enhanced by suxamethonium, leading to enhanced ventricular excitability.









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Temazepam

Uses

Temazepam is used:

1. as a hypnotic and
2. for anaesthetic premedication.

Chemical

A 3-hydroxy benzodiazepine which is a minor metabolite of diazepam.



Presentation

As tablets containing 10/20 mg and an elixir containing2 mg/ml of temazepam.

Main action

Temazepam has anxiolytic, hypnotic, anticonvulsant, and muscle relaxant properties.

Mode of action

Benzodiazepines are thought to act via specific benzodiazepine receptors found at synapses throughout the central nervous system, but concentrated especially in the cortex and midbrain. Benzodiazepine receptors are closely linked with GABA receptors and appear to facilitate the activity of the latter. Activated GABA receptors open chloride ion channels which then either hyperpolarize or short-circuit the synaptic membrane.

Route of administration/doses

Temazepam is administered orally; the adult dose is 10–60 mg.

Effects

CVS

Benzodiazepines have minimal effects on cardiovascular parameters; an insignificant decrease in blood pressure may occur. Benzodiazepines can dilate coronary blood vessels whilst simultaneously reducing myocardial oxygen consumption.

RS

High doses (40 mg) decrease the ventilatory response to hypercapnia.

CNS

The drug causes muscular relaxation, sedation, hypnosis, and anxiolysis; it also has anticonvulsant properties.

Metabolic/other

High doses (40 mg) cause a slight fall in temperature.

Toxicity/side effects

Temazepam is normally well tolerated; gastrointestinal upsets, headaches, dreams, paraesthesiae, and a ‘hangover effect’ (in 10–15%) may occur. Tolerance and dependence may occur with prolonged use of benzodiazepines; acute withdrawal of benzodiazepines in these circumstances may produce insomnia, anxiety, confusion, psychosis, and perceptual disturbances.

Kinetics

Absorption

Absorption of oral temazepam is virtually complete; antacidsdelay the absorption of benzodiazepines.

Distribution

Temazepam is 76% protein-bound *in vivo*. The V_D is 0.8 l/kg.

Metabolism

The drug is predominantly metabolized in the liver by direct conjugation to glucuronide; active metabolites are not formed to any great extent

Excretion

80% of an administered dose appears in the urine as inactive conjugates; 12% is excreted in the faeces. The clearance is 6.6 l/hour and the elimination half-life is 5–11 hours.

Special points

The drug is not removed by haemodialysis. Temazepam is a drug of abuse and has controlled drug status.

Terbutaline

Uses

Terbutaline is used in the treatment of:

1. asthma
2. chronic obstructive airways disease and
3. uncomplicated preterm labour.

Chemical

An alcohol.

Presentation

As 5 mg tablets, a syrup containing 0.3 mg/ml, a clear solution for injection containing 0.5 mg/ml, a respirator solution containing 2.5/10 mg/ml, and as an inhaler delivering 0.5 micrograms per actuation of terbutaline sulphate. It can be administered intravenously or subcutaneously 250–500 micrograms 6-hourly, and by infusion at a rate up to 5 micrograms/min in adults.

Main action

Bronchodilatation and uterine relaxation.

Mode of action

Terbutaline is a beta-adrenergic agonist (with a more pronounced effect at beta-2 than beta-1 receptors) that acts by stimulation of membrane-bound adenyl cyclase in the presence of magnesium ions to increase intracellular cAMP concentrations.

Route of administration/doses

The adult oral dose is 2.5–5 mg 8-hourly; the subcutaneous, intramuscular, and intravenous dose is 0.25–0.5 mg once or twice a day. Terbutaline may be administered by intravenous infusion diluted in glucose or saline at the rate of 1.5–5 micrograms/min for 8–10 hours. The dose by inhalation is 0.25–0.5 micrograms 4-hourly or 2–5 mg 8–12-hourly if nebulized.

Effects

CVS

When used in large doses, terbutaline has positive inotropic and chronotropic effects.

RS

Bronchodilatation, leading to an increased PEFR and FEV1, occurs after administration of the drug. This is additive to the bronchodilatation produced by phosphodiesterase inhibitors. The drug interferes with the mechanism of hypoxic pulmonary vasoconstriction; an adequate inspired oxygen concentration should be ensured when terbutaline is used.

GU

Terbutaline relaxes uterine musculature. An increased tendency to bleeding has been reported in association with Caesarean section.

Metabolic/other

Hyperinsulinaemia, leading to hypoglycaemia and hypokalaemia, may follow administration of the drug. Antepartum administration of terbutaline stimulates release of surface-active material into the alveolar space of the fetus, improving the function of the neonatal lung.

Toxicity/side effects

Tremor, palpitations, cramps, anxiety, and headache occur uncommonly after the administration of terbutaline.

Kinetics

Absorption

The drug is incompletely absorbed after oral administration; the bioavailability is 7–26%. Less than 10% is absorbed after inhalation, the remainder being swallowed.

Distribution

Terbutaline is 25% protein-bound in the plasma; the V_D is 1.6 l/kg.

Metabolism

Terbutaline has an extensive first-pass metabolism; the drug is predominantly metabolized to a sulphate conjugate.

Excretion

60–70% is excreted unchanged in the urine, the remainder as the sulphated conjugate. The clearance is 1.75–2.75 ml/min/kg and the elimination half-life is 11.5–23 hours.

Tetracycline

Uses

Tetracycline is used in the treatment of infections of:

1. the respiratory, gastrointestinal, and urinary tracts
2. ear, nose, and throat
3. soft tissues and in the treatment of
4. venereal diseases, including non-specific urethritis
5. typhus fever
6. psittacosis
7. cholera
8. acne rosacea and for
9. the treatment of recurrent pleural effusions and
10. the prophylaxis of subacute bacterial endocarditis.

Chemical

A napthacenecarboxamide derivative.

Presentation

As 250 mg tablets, a syrup containing 25 mg/ml, in vials containing 100 mg (with procaine) for intramuscular injection, and 250/500 mg (with ascorbic acid) for intravenous injection of tetracycline hydrochloride. An ointment for topical use is also available.

Main actions

Tetracycline is a broad-spectrum bacteriostatic antibiotic which is active against Gram-positive and Gram-negative bacteria, including *Clostridium*, *Streptococcus*, *Neisseria*, *Brucella*, and *Vibrio* spp., *Haemophilus influenzae*, *Yersinia pestis*, and *Rickettsiae*, *Mycoplasma*, *Chlamydia*, *Leptospira*, and *Treponema* spp.

Mode of action

Tetracycline inhibits bacterial protein synthesis by binding to bacterial 30S ribosomes (in the same manner as do aminoglycosides) and preventing the access of aminoacyl tRNA to the mRNA-ribosome complex, thereby preventing further elongation of the polypeptide chain.

Routes of administration/doses

The adult oral dose is 250–500 mg 6-hourly. The corresponding intramuscular dose is 100 mg 4–8-hourly and the intravenous dose is 0.5–1 g 12-hourly. The intrapleural dose is 500 mg (of the intravenous preparation). Intramuscular injection of the drug is painful.

Effects

CVS

Tetracycline may increase intracranial pressure.

Metabolic/other

The drug may cause an increase in the plasma urea concentration and decrease the plasma prothrombin activity.

Toxicity/side effects

Occur in 1–5% of patients. The drug may cause renal and hepatic impairment, gastrointestinal and haematological disturbances, moniliasis, rashes, photosensitivity, and thrombophlebitis. Tetracycline may also cause tooth staining in infancy.

Kinetics

Absorption

Tetracycline is incompletely absorbed when administered orally (it chelates with iron, calcium, and aluminium in the gut). The bioavailability is 77% by the oral route.

Distribution

The drug is widely distributed and exhibits good tissue penetration. The drug is 62–68% protein-bound in the plasma; the V_D is 0.75–1.37 l/kg.

Metabolism

5% of the dose is metabolized to epitetracycline, the remainder is excreted unchanged.

Excretion

95% of the dose is excreted unchanged; 60% is excreted in the urine by glomerular filtration, the remainder in the faeces. The clearance is 1.43–1.91 ml/min/kg and the half-life is 10–16 hours. A decreased dose should be used in the presence of renal failure.

Special points

Tetracycline has been demonstrated to increase the action of non-depolarizing relaxants. It is pharmaceutically incompatible with a host of other drugs, including thiopental, sodium bicarbonate, and autologous blood.

Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines with similar side effects. It is used for complicated intra-abdominal, and skin and soft tissue infections. It is active against MRSA and VRE.

Thiopental

Uses

Thiopental is used:

1. for the induction of anaesthesia
2. in the management of status epilepticus and has been used
3. for brain protection.

Chemical

A thiobarbiturate.

Presentation

As a hygroscopic yellow powder, containing thiopental sodium and 6% sodium carbonate stored under an atmosphere of nitrogen. The drug is reconstituted in water prior to use to yield a 2.5% solution with a pH of 10.8 and pKa of 7.6 which is stable in solution for 24–48 hours.

Main actions

Hypnotic and anticonvulsant.

Mode of action

Barbiturates are thought to act primarily at synapses by depressing post-synaptic sensitivity to neurotransmitters and by impairing pre-synaptic neurotransmitter release. Multi-synaptic pathways are depressed preferentially; the reticular activating system is particularly sensitive to the depressant effects of barbiturates. The action of barbiturates at the molecular level is unknown. They may act in a manner analogous to that of local anaesthetic agents by entering cell membranes in the unionized form, subsequently becoming ionized and exerting a membrane-stabilizing effect by decreasing sodium and potassium ion conductance, decreasing the amplitude of the action potential, and slowing the rate of conduction in excitable tissue. In high concentrations, barbiturates depress the enzymes involved in glucose oxidation, inhibit the formation of ATP, and depress calcium-dependent action potentials. They also inhibit calcium-dependent neurotransmitter release and enhance chloride ion conductance in the absence of GABA.

Routes of administration/doses

The dose by the intravenous route is 2–7 mg/kg; following bolus administration, thiopental acts in one arm–brain circulation time and lasts for 5–15 minutes; it is cumulative with repeated administration. The drug may also be administered rectally in a dose of 1 g/22 kg body weight when it acts within 15 minutes.

Effects

CVS

Thiopental is a negative inotrope and decreases cardiac output by approximately 20%; the blood pressure usually decreases as a result of both this effect and a decrease in systemic vascular resistance.

RS

Thiopental is a potent respiratory depressant; following intravenous administration, a period of apnoea may occur, followed by a more prolonged period of respiratory depression with a decrease in the ventilatory response to hypercapnia. Laryngeal spasm is occasionally seen in association with the administration of thiopental; the drug may also produce a degree of bronchoconstriction.

CNS

Thiopental produces a smooth, rapid induction of anaesthesia. Cerebral blood flow, intracranial pressure, and intraocular pressure are all decreased after the administration of the drug. As with all barbiturates, thiopental has anticonvulsant properties. The drug is antanalgesic when used in small doses. The characteristic EEG changes observed after thiopental administration are initially a fast activity which is subsequently replaced by synchronized low-frequency waves.

AS

The drug causes some depression of intestinal activity and constriction of the splanchnic vasculature.

GU

Thiopental decreases renal plasma flow and increases ADH secretion, leading to a decrease in urine output. It has no effect on the tone of the gravid uterus.

Metabolic/other

A slight transient decrease in the serum potassium concentration may occur following the administration of thiopental.

Toxicity/side effects

Severe anaphylactoid reactions may occur with the use of the drug with a reported incidence of 1 in 20 000. Extravasation of the drug may lead to tissue necrosis; inadvertent intra-arterial injection may lead to arterial constriction and thrombosis. The treatment of the latter includes the administration of analgesia and alpha-adrenergic antagonists, sympathetic blockade of the limb, and anticoagulation.

Kinetics

Absorption

Thiopental is absorbed when administered orally or rectally.

Distribution

The drug is 65–86% protein-bound in the plasma, predominantly to albumin; 40% is sequestered in red blood cells; the V_D is 1.96 l/kg. The rapid onset of action of the drug is due to:

1. the high blood flow to the brain
2. the lipophilicity of the drug and
3. its low degree of ionization—only the non-ionized fraction crosses the blood–brain barrier (thiopental is 61% non-ionized at pH 7.4; hyperventilation increases the non-bound fraction and increases the anaesthetic effect).

The relatively brief duration of anaesthesia following a bolus of thiopental is due to redistribution to muscle and later to fat.

Metabolism

Occurs in the liver by side-arm oxidation, oxidation to pentobarbital, and ring cleavage to form urea and 3-carbon fragments. 15% of the dose of the drug is metabolized per hour; 30% may remain in the body 24 hours after administration.

Excretion

Occurs predominantly in the urine as inactive metabolites; 0.5% is excreted unchanged. The clearance is 2.7–4.1 ml/kg/min and the elimination half-life is 3.4–22 hours.

Special points

Volatile agents and surgery have no effect on the V_D or clearance of thiopental; morphine increases the hypnotic effect of the drug and increases its brain half-life. The drug may induce acute clinical and biochemical manifestations in patients with porphyria. Thiopental should be used with caution in patients with fixed cardiac output states, hepatic or renal dysfunction, myxoedema, dystrophia myotonica, myasthenia gravis, familial periodic paralysis, and in the elderly or in patients who are hypovolaemic.

Thiopental is not removed by dialysis.

Thrombolytics

Uses

Thrombolytic agents are used:

1. in the treatment of acute myocardial infarction
2. in the treatment of acute ischaemic cerebrovascular events (alteplase only)
3. for the intravascular dissolution of thrombi and emboli (e.g. deep vein thrombosis and massive pulmonary embolism (alteplase only)) and
4. in the treatment of acute or subacute occlusion of peripheral arteries.

Chemical

Thrombolytic agents are (glyco)protein structures that are either obtained from bacteria or genetically engineered. Streptokinase is a highly purified enzyme derived from beta-haemolytic streptococci of Lancefield Group C. Alteplase, reteplase, and tenecteplase are derived fromChinese Hamster Ovary cell lines using recombinant DNA technology.

Presentation

Streptokinase, alteplase, reteplase, and tenecteplase are all presented in a powder form requiring subsequent dissolving prior to intravenous injection and/or infusion depending on the specific agent.

Main action

Fibrinolysis.

Mode of action

Alteplase, reteplase, and tenecteplase are recombinant human tissue plasminogen activators (rtPA) that are fibrin-specific. These agents bind to fibrin within the thrombus

with subsequent conversion of thrombus-bound plasminogen to plasmin, leading to fibrin degradation. Streptokinase acts indirectly on plasmin; the first phase is the formation of a streptokinase–plasminogen activator complex, which then converts further plasminogen molecules to active plasmin. Plasmin then digests fibrin to produce lysis of thrombi.

Route of administration/doses

Thrombolytic agents are administered intravenously. This may be by bolus injection only followed by further boluses and/or an intravenous infusion, depending on the type of agent being used and the regimen being followed. Streptokinase is administered by intravenous infusion. Alteplase is administered by a bolus followed by infusion using either an 'accelerated' or a 'standard' regimen for acute myocardial infarction. For the treatment of pulmonary embolism, alteplase is administered as a 10 mg bolus over 1–2 minutes followed by 90 mg over 2 hours. For the treatment of acute ischaemic stroke, alteplase is given over 1 hour at a dose of 0.9 mg/kg (maximum dose of 90 mg) with 10% of the dose given as a bolus. Tenecteplase is administered by a single weight adjusted bolus and reteplase is administered as two boluses 30 minutes apart.

Effects

CVS

Transient hypotension and reperfusion arrhythmias may occur following administration of thrombolytic agents.

Metabolic/other

Fibrinolysis is produced by the action of the drug on plasmin. Following administration of streptokinase, anti-streptokinase antibodies are produced.

Toxicity/side effects

Excessive haemorrhage may complicate the use of any thrombolytic agent; if serious, this should be treated by cessation of drug administration, resuscitation, and possible treatment with intravenous tranexamic acid. The risk of a haemorrhagic cerebrovascular event is 0.5–1%. Pyrexia occurs commonly following administration of streptokinase. Allergic reactions are common with the use of streptokinase, which can be minimized with the administration of antihistamines and corticosteroids.

Kinetics

Data are incomplete.

Distribution

The V_D of thrombolytic agents are low: streptokinase 1.1 l, alteplase 2.8–4.6 l, reteplase 6 l, and tenecteplase 4.2–6.3 l.

Metabolism

Thrombolytic agents undergo hepatic metabolism. Tenecteplase binds to specific hepatic receptors prior to conversion into small peptides.

Excretion

The terminal elimination half-life of streptokinase is 83 minutes. Alteplase, reteplase, and tenecteplase undergo biphasic elimination. Alteplase is rapidly cleared from the plasma with a plasma clearance of 550–680 ml/min. Reteplase and tenecteplase are cleared more slowly with plasma clearance data of approximately 120 ml/min.

Special points

Heparin is administered with all thrombolytic agents apart from streptokinase. Due to the bolus dose administration of reteplase and tenecteplase, these agents are used in pre-hospital thrombolysis in addition to in-hospital use.

The current National Service Framework for thrombolysis for myocardial infarction states a 'call to needle' time of 60 minutes and a 'door to needle time' of 20 minutes. If the 'call to hospital' time is greater than 30 minutes, then pre-hospital thrombolysis should be considered. Thrombolytic agents should not be administered to patients with contraindications to thrombolysis as detailed in national guidelines and/or local policies.

Tramadol

Uses

Tramadol is used in the management of moderate to severe pain.

Chemical

A synthetic opioid of the aminocyclohexanol group. The drug is a racemic mixture of two enantiomers, (+) and (–) tramadol.

Presentation

As a clear aqueous solution for injection containing 50 mg/ml and tablets containing 50/100/150/200/300/400 mg of tramadol hydrochloride.

Main action

Centrally mediated analgesia.

Mode of action

Tramadol is a non-selective agonist at mu-, kappa-, and delta-opioid receptors (with a higher relative affinity for mu-receptors). It also inhibits neuronal reuptake of noradrenaline and enhances serotonin (5HT) release; inhibition of pain perception partly involves the activation of descending serotonergic and noradrenergic pathways.

Route of administration/doses

Tramadol may be administered orally, intramuscularly, or by slow intravenous injection or infusion. The adult dose is 50–100 mg 4–6-hourly for all routes of administration.

The paediatric dose is 1–2 mg/kg 4–6-hourly.

Effects

CVS

Tramadol has no clinically significant cardiovascular effects after intravenous administration.

RS

Respiratory rate, minute volume, and $PaCO_2$ remain essentially unchanged following intravenous administration of therapeutic doses of the drug.

CNS

Tramadol has an analgesic potency equivalent to pethidine. The analgesic effect is only partially (30%) reversed by naloxone.

AS

Tramadol has no demonstrable effect on bile duct sphincter activity. Constipation occurs uncommonly.

Toxicity/side effects

The principal side effects of tramadol are nausea, dizziness, sedation, and diaphoresis. The potential for tolerance and dependence appears to be low.

Kinetics

Absorption

The bioavailability following oral administration of the drug is 68–100%.

Distribution

The drug is 20% protein-bound in the plasma; the V_D is 2.9–4.37 l/kg. 80% of an administered dose crosses the placenta.

Metabolism

85% of an administered dose is metabolized by demethylation in the liver. One metabolite (O-desmethyltramadol) is active.

Excretion

90% of the dose is excreted in the urine and 10% in the faeces. The clearance is 6.7–10.1 ml/kg/min and the elimination half-life is 270–450 minutes. The elimination half-life is doubled in patients with impaired renal or hepatic function.

Special points

The use of tramadol is not recommended in patients with end-stage renal failure; the dosage interval should be increased to 12 hours in patients with renal or hepatic impairment.

The drug is not licensed for intraoperative use as it may enhance intraoperative recall during enflurane/nitrous oxide anaesthesia.

Tramadol appears to be effective in the treatment of post-operative shivering.

The drug precipitates when mixed with diazepam or midazolam. The drug is only slowly removed by haemodialysis or haemofiltration.

Trichloroethylene

Uses

Trichloroethylene is used:

1. for the induction and maintenance of general anaesthesia and has been used
2. for pain relief during labour.

Chemical

A halogenated hydrocarbon.

Presentation

As a blue liquid (that should be protected from light) that is coloured with waxoline blue to enable differentiation from chloroform. The commercial preparation contains 0.01% thymol which prevents decomposition on exposure to light; it is non-flammable in normal anaesthetic concentrations. The molecular weight of trichloroethylene is 131.4, the boiling point 67°C, and the saturated vapour pressure is 8kPa at 20°C. The MAC of trichloroethylene is 0.17, the oil/water solubility coefficient 400, and the blood/gas solubility coefficient 9.

Main action

General anaesthesia (reversible loss of both awareness and recall of noxious stimuli) and analgesia.

Mode of action

The mechanism of general anaesthesia remains to be fully elucidated. General anaesthetics appear to disrupt synaptic transmission (especially in the area of the ventrobasal thalamus), predominantly by inhibiting neurotransmitter release and by interfering with the interaction of neurotransmitters with post-synaptic receptors. Their mode of action at the molecular level appears to involve expansion of hydrophobic regions in the neuronal membrane, either within the lipid phase or within hydrophobic sites in cell membrane proteins.

Route of administration/doses

Trichloroethylene is administered by inhalation, conventionally via a calibrated vaporizer. The concentration used for the induction and maintenance of anaesthesia is 0.2–2%.

Effects

CVS

Trichloroethylene is noted for its cardiovascular stability; the heart rate, blood pressure, and cardiac output are little altered by the administration of the drug. Trichloroethylene has a marked propensity to cause dysrhythmias and sensitizes the myocardium to the effects of circulating catecholamines.

RS

The drug is moderately irritant to the respiratory tract and characteristically causes tachypnoea associated with a decreased tidal volume which may lead to both hypoxia and hypercapnia.

CNS

The principal effect of trichloroethylene is general anaesthesia; the drug also has a marked analgesic effect. The drug increases cerebral blood flow, leading to an increase in intracranial pressure. A slight decrease in skeletal muscle tone results from the use of trichloroethylene.

AS

Nausea and vomiting occur commonly with the use of the drug.

GU

Trichloroethylene reduces the tone of the pregnant uterus when used in concentrations 0.5%.

Toxicity/side effects

Trichloroethylene may provoke the appearance of myocardial dysrhythmias, particularly in the presence of hypoxia, hypercapnia, or excessive catecholamine concentrations.

Kinetics

Absorption

The major factors affecting the uptake of volatile anaesthetic agents are solubility, cardiac output, and the concentration gradient between the alveoli and venous blood. Trichloroethylene is relatively soluble in blood; alveolar concentration, therefore, reaches inspired concentration relatively slowly, resulting in a slow induction of anaesthesia. An increase in the cardiac output increases the rate of alveolar uptake and slows the induction of anaesthesia. The concentration gradient between alveoli and venous blood approaches zero at equilibrium; a large concentration gradient favours the onset of anaesthesia.

Distribution

The drug is initially distributed to organs with a high blood flow (the brain, heart, liver, and kidney) and later to less well-perfused organs (muscles, fat, and bone).

Metabolism

20% of an administered dose is metabolized in the liver to yield trichloroacetic acid, monochloroacetic acid, and trichloroethanol (which is subsequently conjugated with glucuronide) and inorganic chloride.

Excretion

80% is exhaled unchanged; the metabolites are excreted in the urine over several days.

Special points

Trichloroethylene should not be used in a closed circuit with soda lime since it decomposes in the presence of heat and alkali to form hydrochloric acid, carbon monoxide, dichloroacetylene, and phosgene, all of which are toxic.







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Vecuronium

Uses

Vecuronium is used to facilitate intubation and controlled ventilation.

Chemical

A bis-quaternary aminosteroid which is the mono-quaternary analogue of pancuronium.

Presentation

As a lyophilized powder (containing citric acid monohydrate (20.75 mg), disodium hydrogen phosphate dihydrate (16.25 mg), mannitol (170 mg), sodium hydroxide or phosphoric acid) which is diluted in water prior to use to yield a clear, colourless, isotonic solution containing 2 mg/ml of vecuronium bromide. Mannitol is used to alter the tonicity and the presence of either sodium hydroxide or phosphoric acid adjusts the pH to 4. The solution is stable for 24 hours.

Main action

Competitive non-depolarizing neuromuscular blockade.

Mode of action

Vecuronium acts by competitive antagonism of acetylcholine at nicotinic (N2) receptors at the post-synaptic membrane of the neuromuscular junction.

The drug also has some pre-junctional action.

Route of administration/doses

The drug is administered intravenously. The ED_{90} of vecuronium is estimated to be 0.057 mg/kg. An initial dose of 0.08–0.1 mg/kg is recommended, providing muscle relaxation for between 25–40 minutes. Endotracheal intubation can be achieved within 90–120 seconds of an intravenous dose with maximal resultant neuromuscular blockade achieved within 3–5 minutes following administration. 95% recovery of the twitch height occurs within approximately 45 minutes. Maintenance of neuromuscular blockade may be achieved with bolus doses of 0.02–0.03 mg/kg. Vecuronium may be administered by intravenous infusion at a rate of 0.8–1.4 micrograms/kg/min. The drug is non-cumulative with repeated administration.

Effects

CVS

Vecuronium has minimal cardiovascular effects; with large doses, a slight (9%) increase in cardiac output and 12% decrease in systemic vascular resistance may occur. Unlike pancuronium, the drug will not antagonize the haemodynamic changes or known side effects produced by other pharmaceutical agents or surgical factors.

RS

Neuromuscular blockade leads to apnoea. Vecuronium has a very low potential for histamine release; bronchospasm is extremely uncommon.

CNS

The drug has no effect on intracranial or intraocular pressure.

AS

Lower oesophageal sphincter pressure remains unaltered after the administration of vecuronium.

Metabolic/other

Vecuronium may decrease the partial thromboplastin time and prothrombin time.

Toxicity/side effects

There have been rare reports of fatal anaphylactoid reactions with the administration of vecuronium. Cross-sensitivity may exist with rocuronium and pancuronium.

Kinetics

Distribution

The drug is 60–90% protein-bound in the plasma. The V_D is 0.18–0.27 l/kg. The drug does not cross the blood–brain barrier. Very small amounts of vecuronium may cross the placenta, but not in clinically significant doses.

Metabolism

Vecuronium is metabolized by deacetylation in the liver to the active metabolites, 3- and 17-hydroxy and 3,17-dihydroxyvecuronium. These metabolites, which in the case of 3-hydroxyvecuronium may have up to 50% of the potency of vecuronium, are present in very low concentrations although may be of clinical significance after prolonged dosing.

Excretion

25–30% of the dose is excreted unchanged in the urine and 20% unchanged in the bile. Metabolized drug is excreted in the bile. The clearance is 3–6.4 ml/kg/min and the elimination half-life is 31–80 minutes. Renal failure leads to a prolongation of the elimination half-life, but to no clinically significant increase in the duration of action of vecuronium. Hepatic failure may cause a significant dose-dependent decrease in the clearance and consequent increase in the duration of action of the drug.

Special points

The duration of action of vecuronium, in common with other non-depolarizing relaxants, is prolonged by hypokalaemia, hypocalcaemia, hypermagnesaemia, hypoproteinaemia, dehydration, acidosis, and hypercapnia. The following drugs, when co-administered with vecuronium, increase the effect of the latter: volatile anaesthetic agents, induction agents (including ketamine), fentanyl, suxamethonium, diuretics, calcium channel blockers, alpha- and beta-adrenergic antagonists, protamine, lidocaine, metronidazole, and the aminoglycoside antibiotics. Patients with burns may develop resistance to the effect of vecuronium. Onset of neuromuscular blockade is likely to be lengthened and the duration of action shortened in patients receiving chronic anticonvulsant therapy. The use of vecuronium appears to be safe in patients susceptible to malignant hyperpyrexia.

Reversal of neuromuscular blocking activity by vecuronium may be achieved using neostigmine (in combination with glycopyrronium), but only after four twitches have returned on the train-of-four count. The gamma-cyclodextrin, sugammadex, may be used to reverse vecuronium-induced neuromuscular blockade by encapsulating vecuronium molecules within the plasma, thereby creating a concentration gradient favouring the movement of remaining vecuronium molecules from the neuromuscular junction back into the plasma.

Verapamil

Uses

Verapamil is used in the treatment of:

1. hypertension of mild to moderate severity
2. angina and
3. paroxysmal supraventricular tachycardia, and atrial fibrillation and flutter.

Chemical

A synthetic papaverine derivative.

Presentation

As 40/80/120/160/180/240 mg tablets and as a clear solution for injection of a racemic mixture of verapamil hydrochloride containing 2.5 mg/ml.

Main actions

Antihypertensive and antianginal.

Mode of action

Verapamil causes competitive blockade of cell membrane slow calcium ion channels, leading to a decreased influx of calcium ions into vascular smooth muscle and myocardial cells. This results in electromechanical decoupling, inhibition of contraction, and relaxation of cardiac and smooth muscle fibres, leading to coronary and systemic arterial vasodilation.

Route of administration/doses

The adult oral dose is 240–480 mg daily in 2–3 divided doses. The corresponding intravenous dose in 5–10 mg administered over 30 seconds; the injection should cease as soon as the desired effect is achieved. The peak effect after intravenous administration occurs at 3–5 minutes and the duration of action is 10–20 minutes.

Effects

CVS



Verapamil is a class IV antiarrhythmic agent; it decreases automaticity and conduction velocity and increases the refractory period. Atrio-ventricular conduction is slowed; the drug appears to be taken up and bound specifically by atrio-ventricular nodal tissue. The drug causes a decrease in the systemic vascular resistance and is a potent coronary artery vasodilator. Verapamil has negative dromotropic and inotropic effects which are enhanced by acidosis.

CNS

Cerebral vasodilation occurs after the administration of verapamil.

GU

Verapamil decreases renovascular resistance.

Toxicity/side effects

Oral administration of the drug may lead to dizziness, flushing, nausea, and first- or second-degree heart block. Intravenous administration may precipitate heart failure in patients with impaired left ventricular function and precipitate ventricular tachycardia or fibrillation in patients with Wolff–Parkinson–White syndrome.

Kinetics

Absorption

Verapamil is completely absorbed when administered orally; the bioavailability is 10–22% due to a significant first-pass.

Distribution

The drug is 90% protein-bound in the plasma; the V_D is 3.1–4.9 l/kg.

Metabolism

Occurs by demethylation and dealkylation in the liver; the metabolites possess some activity.

Excretion

70% of the dose is excreted in the urine and 16% in the faeces. The clearance is 6.8–16.8 ml/min/kg and the elimination half-life is 3–7 hours. The dose should be reduced in patients with significant hepatic impairment.

Special points

The effects of volatile agents and beta-adrenergic antagonists on myocardial contractility and conduction are synergistic with those of verapamil; caution should be exercised when these combinations are used. The drug increases the serum concentrations of co-administered digoxin.

Verapamil and dantrolene administered concurrently in animals cause hyperkalaemia, leading to ventricular fibrillation; these drugs are not recommended for use together in man. The drug decreases the MAC of halothane in animal models; chronic exposure to the drug may potentiate the actions of both depolarizing and non-depolarizing relaxants. Verapamil attenuates the pressor response to laryngoscopy and intubation.

Verapamil is not removed by haemodialysis.







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Warfarin

Uses

Warfarin is used:

1. in the prophylaxis of systemic embolization in patients with rheumatic heart disease and atrial fibrillation and in patients with prosthetic heart valves and
2. in the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism.

Chemical

A synthetic coumarin derivative.

Presentation

As tablets containing 0.5/1/3/5 mg of a racemic mixture of warfarin sodium.

Main actions

Anticoagulation.

Mode of action

Warfarin prevents the synthesis of the vitamin K-dependent clotting factors (II, VII, IX, and X) in the liver. The formation of fully active clotting factors is dependent on the carboxylation of their precursor proteins; during this reaction, vitamin K is oxidized to vitamin K 2,3-epoxide; warfarin prevents the reduction of this epoxide back to vitamin K. This results in vitamin K depletion and a decrease in the rate of formation of complete clotting factors. The S-enantiomer is 2–5 times more potent than the R-enantiomer.

Route of administration/doses

The adult oral dose is usually 3–9 mg/day, according to response as measured by the prothrombin time. The maximum anticoagulant effect occurs 18–72 hours after the administration of a loading dose.

Effects

Warfarin has no clinically significant effects other than its anticoagulant effect.

Toxicity/side effects

Haemorrhage is the most frequent side effect. Hypersensitivity reactions and gastrointestinal upsets may occur. The drug appears to be teratogenic if taken during pregnancy.

Kinetics

Absorption

The drug is rapidly and completely absorbed from the stomach and upper gastrointestinal tract and has an oral bioavailability of 100%.

Distribution

Warfarin is 99% protein-bound in the serum, predominantly to albumin. The V_D is 0.1–0.16 l/kg.

Metabolism

Warfarin is virtually completely metabolized in the liver by oxidation (of the L-form) and reduction (of the D-form); these metabolites are then conjugated with glucuronide

Excretion

The metabolites are excreted in the faeces and urine. The clearance is 3.26–3.8 ml/min/kg and the elimination half-life of warfarin ranges from 35 to 45 hours; this is decreased in patients with renal impairment.

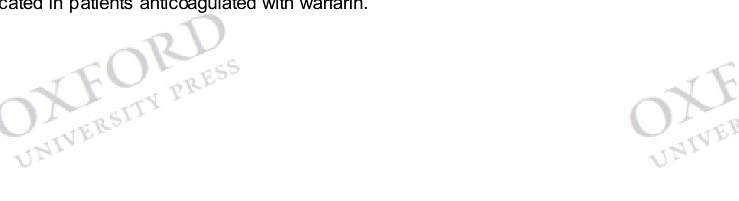
Special points

The response to warfarin treatment is monitored in the laboratory by the one-stage prothrombin time which is particularly sensitive to the activity of factors II, VII, and X. The INR should be maintained at 2–4.5 times the control value. Many factors may affect warfarin control; in particular, the drug may exhibit significant interactions with many other drugs. The activity of warfarin may be potentiated by alcohol, amiodarone, cimetidine, sulphonamides, salicylates and other NSAIDs, and many antibiotics, including co-trimoxazole, erythromycin, chloramphenicol, metronidazole, and tetracyclines. The activity of warfarin may be decreased by many drugs, including barbiturates, the oral contraceptive pill, and carbamazepine.

Control of anticoagulation in the perioperative period requires special attention. This is usually achieved by transferring the patient to heparin prior to and immediately after surgery; the INR should ideally be less than 2 for routine surgery. Acute reversal of the effects of warfarin can be achieved by the administration of prothrombin complex, especially in cases of life-threatening haemorrhage. Alternatively, 1 mg of vitamin K will reverse its effects within 12 hours and 10 mg will prevent re-warfarinization

due to the saturation of liver stores.

Spinal and epidural anaesthesia are contraindicated in patients anticoagulated with warfarin.





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